IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

- - -

IN RE BENDAMUSTINE CONSOLIDATED CASES) Civil Action No. 13-2046
) CONSOLIDATED

- - -

Wilmington, Delaware
Monday, December 7, 2015
9:00 a.m.
Trial Day 5

- - -

BEFORE: HONORABLE GREGORY M. SLEET, U.S.D.C.J.

APPEARANCES:

SARA BUSSIERE, ESQ.
Bayard, PA
-and-
KAREN E. KELLER, ESQ.
Shaw Keller LLP
-and-
PAUL F. WARE, ESQ.,
CALVIN E. WINGFIELD, JR., ESQ.,
DARYL L. WIESEN, ESQ.,
EMILY L. RAPALINO, ESQ., and
NICHOLAS K. MITROKOSTAS, ESQ.
Goodwin Procter LLP
(Boston, MA)

Counsel for Cephalon, Inc.

STAMATOS STAMOULIS, ESQ.
Stamoulis & Weinblatt LLC
-and-
JOSEPH E. CWIK, ESQ., and
JONATHAN URIT, ESQ.
Amin Talati & Upadhye
(Chicago, IL)

Counsel for InnoPharma, Inc.

APPEARANCES CONTINUED:

MELANIE K. SHARP, ESQ., and
SAMANTHA G. WILSON, ESQ.
Young Conaway Stargatt & Taylor LLP
-and-
:17:01 **SARAH TONNIES HORTON, ESQ., and**
YUSUF ESAT, ESQ.
Jenner & Block LLP
(Chicago, IL)

Counsel for Hospira, Inc.

NEAL C. BELGAM, ESQ.
Smith Katzenstein & Jenkins LLP
-and-
AZY S. KOKABI, ESQ.,
MICHAEL R. DZWONCZYK, ESQ., and
ALTON HARE, ESQ.
Sughrue Mion PLLC
(Washington, D.C.)

Counsel for Accord Healthcare Inc. And Intas Pharmaceuticals

JOHN M. SEAMAN, ESQ.
Abrams & Bayliss LLP
-and-
A. NEAL SETH, ESQ.,
LAWRENCE M. SUNG, ESQ., and
KARIN A. KESSLER, ESQ.
Wiley Rein LLP
(Washingon, D.C.)

Counsel for Hetero Labs Ltd. and Hetero USA, Inc.

SHANTI M. KATONA, ESQ.
Polsinelli PC
-and-
RONALD M. DAIGNAULT, ESQ., and
RICHARD JUANG, ESQ.
Polsinelli PC
(New York, NY)

Counsel for Sagent Pharmaceuticals, Inc.

:12:23 **THE COURT: Good morning. Please, take your**
:12:25 **seats.**
:12:27 **All right. Mr. Wiesen.**
:12:28 **MR. WIESEN: Good morning, Your Honor. I wanted**
:12:31 **to give you a brief overview of how I think both parties see**
:12:34 **the remainder of the case running, so you would have a**
:12:37 **little bit of a mindset for what we will do today.**
:12:39 **The plaintiffs will start with Dr. Winter, who**
:12:41 **is our expert on lyophilization, and will respond on some of**
:12:44 **the technique arguments. And then we will present Dr.**
:12:47 **Grabowski, who is an economist from Duke, on secondary**
:12:50 **considerations concerning commercial success. You may be**
:12:53 **familiar with Dr. Grabowski.**
:12:55 **THE COURT: I believe I am.**
:12:56 **MR. WIESEN: Those are the only two witnesses we**
:12:59 **have for today. We expect the day will end somewhat early.**
:13:02 **Tomorrow, the defendants are planning to call I**
:13:07 **believe three witnesses concerning secondary considerations,**
:13:12 **Dr. Ambinder, who is an oncologist -- and if I fail to**
:13:14 **describe it accurately, let me know -- Dr. Jarosz again, and**
:13:17 **then Mr. Hofmann, who is on secondary considerations and**
:13:22 **commercial success. Again, we expect the day will not run a**
:13:26 **full day tomorrow.**
:13:27 **MR. CWIK: That's correct, Your Honor.**
:13:28 **THE COURT: Let's gets started.**

:13:31 **MR. WIESEN: Mr. Mitrokostas will present the**
:13:34 **first witness.**
:13:35 **THE COURT: Mr. Mitrokostas.**
:13:36 **MR. MITROKOSTAS: Good morning, Your Honor.**
:13:37 **THE COURT: Good morning.**
:13:38 **MR. MITROKOSTAS: We would like to call to the**
:13:41 **stand Dr. Gerhard Winter on behalf of the plaintiff**
:13:45 **Cephalon.**
:13:46 **THE COURT: Okay.**
:14:01 **... GERHARD WINTER, having been duly sworn as a**
:14:11 **witness, was examined and testified as follows ...**
:14:18 **THE COURT: Good morning, Doctor.**
:14:21 **THE WITNESS: Good morning.**
:14:21 **DIRECT EXAMINATION**
:14:22 **BY MR. MITROKOSTAS:**
:14:25 Q. **Good morning, Dr. Winter.**
:14:27 **Can you please introduce yourself to the Court?**
:14:30 A. **Yes. My name is Gerhard Winter.**
:14:33 Q. **Where do you live?**
:14:34 A. **I live in Penzberg, a small town south of Munich,**
:14:41 **Germany.**
:14:41 Q. **Where are you employed, Dr. Winter?**
:14:42 A. **I am employed at the University of Munich.**
:14:45 Q. **Is the university known by another name?**
:14:49 A. **Yes. It's called the Ludwig-Maximilians University.**

:14:52 Q. **Is it all right if we refer to it today as LMU?**
:14:56 A. **It's okay.**
:14:56 Q. **What is your title at LMU?**
:15:00 A. **My title is full professor for pharmaceutical**
:15:05 **technology and biopharmaceutics.**
:15:08 Q. **What is pharmaceutical technology, generally?**
:15:12 A. **Pharmaceutical technology applies science to formulate**
:15:17 **drug substances into ready-to-apply formulations, like**
:15:23 **tablets, capsules, ointments, injection solutions,**
:15:28 **lyophilisates, and so on.**
:15:29 Q. **What are your responsibilities as a professor at LMU?**
:15:34 A. **My responsibilities are teaching, research, and, of**
:15:39 **course, some management of these functions as well.**
:15:42 Q. **What types of courses do you teach?**
:15:49 A. **I teach undergraduate and graduate courses in pharmacy**
:15:54 **and pharmacy sciences that range from the more simple**
:16:00 **formulation aspects up to complicated drug delivery issues.**
:16:03 Q. **Do you understand that this case relates to a**
:16:07 **lyophilized pharmaceutical product?**
:16:08 A. **I understand that, yes.**
:16:09 Q. **Is lyophilization the subject matter of any of the**
:16:12 **courses that you teach?**
:16:13 A. **Yes, it is the subject matter of several of those**
:16:16 **courses.**
:16:16 Q. **Besides teaching courses, you mentioned that you also**

perform research. What are your primary research areas?
A. I do a number of research areas. The most important ones are drying technologies, formulation of protein and peptide drugs, depo systems and colloidal drug carriers.
Q. Is your group known for any particular area of research?
A. I think we are known for protein/peptide formulations and as well we are quite well known for lyophilization.
Q. If we could take a step back for a moment and focus on your educational background. From what institution did you did he receive your undergraduate degree?
A. From the University of Heidelberg, Germany.
Q. When did you receive that degree?
A. In 1982.
Q. And what subject matter was that degree?
A. In pharmacy.
Q. Did you receive a graduate degree?
A. Yes. I received a Ph.D. from the same university.
Q. When did you receive your Ph.D.?
A. In 1987.
Q. In what subject matter was your Ph.D.?
A. It was in pharmaceutical technology and biopharmaceutics.
Q. When was the first time that you ever used lyophilization?

A. **I think this was already in the course of my undergraduate studies, maybe in the year 1980.**

Q. **Did you use lyophilization as a Ph.D. student?**

A. **Yes. I used that in the course of my teaching obligations for undergraduates during those years.**

Q. **What did you do after you received your Ph.D., Dr. Winter?**

A. **I went to industry, and more particularly, I went to Merck in Germany.**

Q. **What was your title when you first joined Merck?**

A. **My title was lab head for pharmaceutical development issues.**

Q. **And for how long were you at Merck?**

A. **I was there for a year.**

Q. **What did you do next?**

A. **I joined Boehringer Mannheim Company in Mannheim, Germany.**

Q. **What was your title when you joined Boehringer Mannheim?**

A. **The title was essentially the same, but the subjects were changed.**

Q. **What were your responsibilities when you first joined Boehringer Mannheim?**

A. **My responsibilities were leading a group of technicians working on liquid and mostly parenteral**

formulations of all kinds of drugs, doing experimental blending, carrying out the experiments with them, analyzing the results and transferring those results to the next level of management, reporting into teams and so on.

Q. Was any of the work that you did on lyophilized pharmaceutical products?

A. Yes. There was a lot -- a significant lot of my work was on lyophilization.

Q. Before you joined Boehringer Mannheim, did that company have any lyophilized pharmaceutical products?

A. Yes, they did. They had quite a tradition in lyophilized dosage forms, and my boss in those years had a strong interest in and experience in that field.

Q. At some point while you were working at Boehringer Mannheim did your title change?

A. Yes. After about five years I was promoted to department head for parenteral and liquid dosage forms for the company.

Q. Generally, what were your responsibilities as department head for parenteral and liquid dosage forms?

A. I had to oversee a group, four to five of those groups. I had done this before. And they were all dedicated to liquid and mostly parenteral dosage forms, including lyophilized products.

Q. Did any of the groups have any responsibilities for

clinical supplies?

A. Yes. One of those five groups had responsibility to manufacture all clinical supplies, formulations, be it ampules, vials, or lyophilized products, for the entire company, up to a batch size level of several 10,000 pieces per batch.

Q. For how long did you serve as department head of this group at Boehringer Mannheim?

A. For about another five years.

Q. And then what happened in your career?

A. I was promoted to deputy head of the pharmaceutical development department, including not only liquid and parenteral dosage forms.

Q. What were your responsibilities as deputy head of the pharmaceutical development department?

A. Besides heading my own group, I was responsible to oversee another large group on solid dosage forms and the third one dealing with clinical supplies, manufacturing and managing the packaging of that stuff to support clinical studies.

Q. During your time at Boehringer Mannheim, did you ever developed a lyophilized pharmaceutical product?

A. Yes, I did this very often.

Q. And approximately how many lyophilized products did you develop the that went onto the market?

A. **There were three that went onto the market during that period.**

Q. **What were those products?**

A. **There were two products containing erythropoietin and one containing a drug called Reteplase. It marketed, in English it was marketed under the name Retevase.**

Q. **Were the active ingredients in those products known as big molecules?**

A. **Yes.**

Q. **Is all of your lyophilization experience in these large molecules?**

A. **No, not at all. Also during that time we had a project on so-called small molecules that had to be lyophilized.**

Q. **At some point during your time at Boehringer Mannheim, was that company acquired?**

A. **Yes, it was. It was acquired, I think, in 1997 by Roche, a Swiss company.**

Q. **And did you stay with Roche after it acquired Boehringer Mannheim?**

A. **Yes. I stayed with Roche until 1999.**

Q. **What did you do after you left Roche?**

A. **When I left Roche in 1999, I was directly appointed and took the position I still have as a full professor at the University of Munich.**

:23:15 Q. **And were you hired into that role as a lifelong**
:23:20 **appointment?**
:23:21 A. **Yes, I was.**
:23:22 Q. **All right. And why did you decide to join LMU as a**
:23:25 **professor?**
:23:26 A. **Two aspects. The first one, that after this merger or**
:23:31 **take over, I was asked to join the headquarters in Basil,**
:23:35 **Switzerland, because they have other plans with me and my**
:23:39 **department.**
:23:40 **And, second -- so I had to do a decision or**
:23:43 **make a decision any way. And in parallel, I was actively**
:23:48 **approached by the University of Munich, whether I might**
:23:52 **consider to join there as a full professor.**
:23:55 Q. **And you mentioned previously that one of the research**
:23:59 **areas of your group is lyophilization. Can you explain how**
:24:03 **your group studies lyophilization?**
:24:05 A. **Yes. I think in three areas, we do this. First, and**
:24:12 **I think most important, we do research on lyophilization as**
:24:17 **such, where we try to improve the knowledge and science**
:24:20 **around and for lyophilization.**
:24:24 **Second, in many other research projects, we**
:24:29 **apply lyophilization to create lyophilized products or**
:24:34 **intermediates, which we then put into, let's say,**
:24:40 **formulations or other contexts.**
:24:42 **And, third, of course, as we do have the**

:24:45 capacity and the knowledge to teach lyophilization in the
:24:48 context of our undergraduate and graduate teaching.
:24:52 Q. Approximately how many students are in your laboratory
:24:56 in any given year?
:24:57 A. Ph.D. students, up to 20 in one year.
:25:02 Q. And do any of those students go to work in the
:25:05 pharmaceutical industry?
:25:07 A. Oh, yes. Almost everyone goes that is finished in my
:25:13 group to industry.
:25:14 Q. And can you give us an example of some of the
:25:17 positions that your students have gone into in the
:25:20 pharmaceutical industry?
:25:21 A. Yes. Just recently, one of my former students got
:25:26 appointed to be the department head at Roche for all
:25:31 parenteral formulations on large molecules. Another
:25:37 colleague has more or less the same position at Boehringer
:25:42 Ingelheim Germany. Another one has been appointed to
:25:45 intermediate management level position at Ciba Geigy in
:25:52 Chicago on pharmaceutics, and there are another couple at
:25:55 Sanofi and Novartis in similar positions as well.
:25:59 Q. Have you ever consulted for pharmaceutical companies
:26:02 on lyophilized products?
:26:04 A. I did and do still very often.
:26:09 Q. In what circumstances have you consulted with
:26:11 pharmaceutical companies on lyophilized products?

A. **I would say in three circumstances. Mainly first where companies approach me and ask me to be there on a more regular basis, maybe offer me a consultancy contract. And then I do consulting regularly over maybe a few years.**

Second, they approach me on top of a problem they have or to consider any aspects around lyophilization.

And, third, I also am on the advisory boards, where many things are discussed, but lyophilization might come up here and there as a topic.

And, fourth, I forgot. At the beginning, I do consult to industry through my participation in a spinoff company we have founded a few years ago.

Q. **What is the name of that company?**

A. **The name is Coriolis Pharma.**

Q. **Do you have any publications, Dr. Winter?**

A. **I do, yes.**

Q. **Approximately how many?**

A. **Should be close to 140 today.**

Q. **And are any of those publications published in peer-reviewed journals?**

A. **I would say probably all are.**

Q. **And do any of your publications relate to lyophilization or lyophilized pharmaceutical products?**

A. **Yes. A large amount, a large number of them relate to**

lyophilization.

Q. Do you serve on the editorial board of any peer-reviewed journals?

A. Yes, I do.

Q. Which journals do you serve on?

A. For example, Journal of Pharmaceutical Sciences, European Journal of Pharmaceutics and Biopharmaceutics.

Q. And do those journals publish articles on lyophilization?

A. Yes, they do, and in particular, the one I mentioned first, Journal of Pharmaceutical Sciences, does a lot on lyophilization.

Q. Have you received any awards over your career for your research?

A. I did, yes.

Q. Can you give us an example of an award that you received?

A. Yes. In the early years, I received a Best Paper Award, and more recently, last year, in fact, our group received this Phoenix Pharma Award in Germany for Pharmaceutic Technology. It's sort of the highest award given in Germany in that area.

Q. And are you the named inventor on any United States patents?

A. I am, yes.

:28:44 Q. **And approximately how many patents have you been named**
:28:48 **an inventor on? How many patent families?**
:28:52 A. **Yes. It should be around 45 plus a few patent**
:28:55 **families.**
:28:55 Q. **Before today have you ever testified as an expert in a**
:28:59 **United States Court?**
:29:00 A. **Not in the United States, no.**
:29:03 Q. **Have you worked with counsel in the past to prepare**
:29:08 **slides and to assist in presenting your testimony today?**
:29:11 A. **I did so.**
:29:12 Q. **All right. Could you please turn to PTX-253 in your**
:29:15 **binder, Dr. Winter.**
:29:17 A. **Yes. Just a second. 260?**
:29:25 Q. **253. I apologize if I misspoke.**
:29:29 A. **All right. I'm not sure I have it here. Is it on the**
:29:47 **screen?**
:29:49 Q. **Yes. Yes, Dr. Winter.**
:29:51 A. **It's hidden behind one of these other exhibits. Sorry**
:29:59 **for that. I have it, of course.**
:30:01 Q. **What is it, Dr. Winter?**
:30:04 A. **It's a short version of my CV.**
:30:05 Q. **And does it accurately provide a summary of your**
:30:09 **educational background and experience?**
:30:11 A. **It does.**
:30:12 **MR. MITROKOSTAS: All right. Your Honor,**

plaintiffs would now tender Dr. Winter as an expert on lyophilization, lyophilized pharmaceutical products, including the research and development of those products.

THE COURT: Mr. Cwik?

MR. CWIK: No objection, your Honor.

THE COURT: The doctor is accepted as an expert in this case.

MR. MITROKOSTAS: Thank you.

BY MR. MITROKOSTAS:

Q. So, Dr. Winter, have you prepared a slide to review the opinions that you are going to be offering in your testimony today?

A. I have done so, yes.

Q. All right. And if we can please go to the next slide, PDX 10-3.

Dr. Winter, what opinions are you going to offer in your testimony today?

A. I'm offering opinions on the following subjects. First of all, that it's my opinion that defendants' experts do oversimplify a lot of aspects around lyophilization. It's further my opinion that there was no motivation to reformulate Ribomustin. There's furthermore my opinion that claims 5 and 1 of the so-called '190 patent are not obvious. That Claim 1 of the so-called '863 patent is not obvious. Claims 1 and 4 of the '756 patent are not obvious. And

claims 1, 3, 5 and 19 through 21 of the so-called '270 patent are not obvious as well.

Q. Which patents, which claims of the '190 patent will you be testifying on, just to clarify for the record?

A. Five and eight.

Q. Now, Dr. Winter, were you in the courtroom last week when Dr. Kwan and Dr. Kamat testified?

A. No, I wasn't.

Q. Have you read the transcripts of their testimony given here last week?

A. I have read these transcripts.

Q. From what perspective were you asked to offer your opinions?

A. I've been asked to express my opinions from the perspective of a so-called POSA, person skilled in the art from 2005.

Q. And have you prepared a slide with that definition that you used?

A. Yes, I have.

Q. If we could pleasing to PDX-10-4.

A. Yes. This is the definition I've prepared.

Q. Are you aware, Dr. Winter, that defendants' experts have proposed a few different definitions for the person of ordinary skill in the art?

A. I'm aware of that, yes.

:33:01 Q. **Did you consider those definitions in forming your**
:33:04 **opinions in this case?**
:33:05 A. **I considered these definitions as well.**
:33:10 Q. **And would the opinions that you are going to offer in**
:33:13 **your testimony today change if the Court were to adopt one**
:33:16 **of the defendants' definitions for the person of ordinary**
:33:18 **skill in the art?**
:33:19 A. **No, it would not change.**
:33:21 Q. **And if we could now turn, Dr. Winter, to the first**
:33:26 **issue that you're addressing in your testimony, your**
:33:30 **responses to Dr. Kwan and Dr. Kamat's background on**
:33:34 **lyophilization.**
:33:35 A. **Yes.**
:33:35 Q. **Do you agree with their background and description of**
:33:40 **lyophilization?**
:33:41 A. **Although I agree with a number of aspects they have**
:33:49 **presented, I do not agree with certain other aspects, and I**
:33:54 **put some major issues up here where it is my opinion that**
:34:02 **Dr. Kwan and Dr. Kamat strongly underestimate the complexity**
:34:07 **and unpredictability of the lyophilization processes.**
:34:13 **It is my opinion that they as well**
:34:17 **underestimate multiple factors that a POSA would consider in**
:34:24 **selecting formulations and solvent systems for such**
:34:29 **lyophilization processes.**
:34:31 **And it's, third, also my opinion that they**

underestimate, strongly underestimate the experimental, the amount of experimentation that is required to design a lyophilized pharmaceutical product.

Q. Now, have you prepared a slide to describe the complexity of lyophilization process, in your opinion?

A. Yes, I did.

Q. And if we can go to the next slide, please, which is PDX-10-7.

Dr. Winter, if you could please explain what is described on this slide.

A. Yes. I have put on this slide considerations and factors that have to be considered when formulating a lyophilized product, so I may just go through these headings.

It's ingredients, you have to consider the solubility of API and excipients. Stability of this API in the solution before lyophilization. And later in the product just below that, we go to the right and the lyophilization cycle or process as it's called as well.

We go to the next line, the vial, the size, the volume and the cake that later results from the drying process we consider.

And I think I can go fast through the rest. Solvent levels, reconstitution time. Regulatory aspects and reconstitution, diluent volume. Those were the factors that

came up to my mind. There might be a few others, but I think this is enough.

Q. Are each of these factors that you described independent from each other?

A. No, they are not.

Q. Can you explain how they are not independent from each other?

A. Yes. I will try to explain that with an example. I think we have prepared that, to make it more clear.

If I may ask for the next slide and maybe the following slide as well.

So to provide an example which is relevant, also in the context of what we are discussing here, I chose to take an example of selecting a certain solvent or changing a solvent, and the slide just illustrates, then we should expect the third factor -- I will go up and down -- take the first one to the right. Solubility probably might go up. Stability of the drug substance in the vial solution, I don't know. It depends on the solvent. Lyophilization cycle time may go down because the solvent may evaporate fast. Solvent levels afterwards may go up as well.

We go to the middle product, stability and cake quality, cake quality, cake structure, it is extremely difficult, it is impossible to predict.

I don't want to continue and take too much time.

:37:18 **I think all of those parameters are interrelated to each**
:37:21 **other. This is the teaching of this slide.**
:37:25 **I am sorry that it's not in color on the big**
:37:27 **screen. But I think the Court can see it on the computer**
:37:32 **quite well.**
:37:32 Q. **Now, Dr. Winter, how would a person of ordinary skill**
:37:38 **in the art in 2005 designing a lyophilized pharmaceutical**
:37:42 **product address each of these interdependent factors that**
:37:45 **you have set forth?**
:37:47 A. **I think the person has to do an experiment, and then**
:37:52 **analyze what he gets, what the effect on these factors is.**
:37:58 **And as I said, they are interrelated, and it should take a**
:38:05 **lot of experiments to find out what dependencies there are**
:38:09 **and how to end up at the desired level or aim.**
:38:13 Q. **Generally, what types of experience would that person**
:38:18 **of ordinary skill in the art have to perform?**
:38:21 A. **Well, we are talking about lyophilized products, so**
:38:26 **experiments are that you have to put together, still on the**
:38:30 **left part, left upper part of this slide, your formulation,**
:38:36 **a solution, you have to freeze-dry that. You have to**
:38:39 **analyze the resulting freeze-dried product. You have to**
:38:44 **store that product for a while, analyze it again to achieve**
:38:48 **so-called stability data. Then put it all together and**
:38:52 **consider whether the next round of experiments or some other**
:38:56 **experiments are needed. And there, step by step in the**

:39:02 iterative process, you come to a result.
:39:02 Q. Prior to doing those experiments, would a person of
:39:05 ordinary skill in the art be able to reasonably predict the
:39:08 impact of one factor on each of these other factors that you
:39:11 set forth?
:39:12 A. It's my opinion that he cannot predict that.
:39:14 Q. Now, one of the factors that you mentioned was the
:39:19 choice of solvent. What was the most commonly used solvent
:39:23 in lyophilization of pharmaceutical products in 2005?
:39:28 A. Without any doubt, it was water.
:39:30 Q. And in your almost 30-year career in lyophilization,
:39:33 have you ever utilized TBA, which you understand is the
:39:39 solvent at issue here, in your work for a marketed
:39:42 pharmaceutical product?
:39:43 A. No, never. Never.
:39:44 Q. During your career, approximately how many marketed
:39:48 pharmaceutical products have you been involved in the
:39:50 development of?
:39:52 A. As I said earlier, three that came to the market
:39:55 during my work at Boehringer, another number that came later
:40:01 to the market when I had left, including my consultancy
:40:06 work. This should be a number between ten and 20, I would
:40:09 say.
:40:09 Q. Now, Dr. Winter, you mentioned that water was the most
:40:15 commonly used solvent in 2005. Would a person of ordinary

skill in the art consider using water as a lyophilization solvent even for water-sensitive drugs?

A. Oh, yes. Absolutely, because this is the main driver to go to lyophilization, that you have a drug that is not long term stable in water.

Q. Can you explain why a person of skill in the art would still consider using water with a water-sensitive drug?

A. Yes. Because water sensitivity is a general term. Of course, this has to do with kinetics. That means it depends on how fast that a drug would degrade in water or an aqueous solution. As you only need a very limited period of time pre-lyo, as we call it in the community, that means in the period when we dissolve this compound until it is frozen and dried, we can very well do that, what you just said, to use water for water-sensitive drugs.

Q. If a person of ordinary skill in the art decided not to use water or decided that the compound was water sensitive, are there other strategies that they could employ in their development?

A. You mean except using water?

Q. Well, aside from using other co-solvents, let's say.

A. Yes. I think we just stuck with water. We, of course, have now to consider formulation aspects and so forth, that an aqueous solution is not water only. Now we can add sterile lyophilizers into that solution. We can

apply different temperatures. We can apply what is most relevant, given different pH values. We could consider, also, alternative drying technologies, except lyophilization.

Q. Dr. Winter, I would like to now turn to the next issue that you are addressing, which should be on Slide 10-10.

Dr. Winter, do you recall Dr. Kwan and Dr. Kamat's testimony that a person of ordinary skill in the art in 2005 would have been motivated to reformulate Ribomustin?

A. I recall this, yes.

Q. Do you agree with them?

A. No, I do not.

Q. Why not?

A. Because I do not see where this motivation to reformulate Ribomustin should come from. I do not see this motivation.

Q. Now, did you consider the prior art references that Dr. Kwan and Dr. Kamat referenced on Ribomustin?

A. Yes, I considered that, yes.

Q. Have you prepared a slide summarizing your opinions on those references?

A. I did so.

Q. If we could have the next slide. Thank you.

Dr. Winter, what were the teachings of Maas to a person of ordinary skill in the art as of 2005 as it relates

to whether there was a problem that would have required Ribomustin to be reformulated?

A. Yes. I summarize here three key disclosures I take from Maas or that Maas has disclosed, which is, first that she discusses the stability of Ribomustin after reconstitution, and in doing so, she reports in the summary that there is no stability problem with Ribomustin, as she gives, hands out to the medical community data that allows, it is very valid to use this drug in the context where it should be used. And she does not at all, she does not even speak about pre-lyophilization solutions.

Q. Since we are discussing the Maas reference, Dr. Winter, if you could please turn to DTX-577 in your binder.

If we could please go to PDX-10-15.

A. Okay.

Q. If you could turn to internal Page 4 of the Maas reference, please.

I would like you to read the last sentence in the second paragraph under Discussion into the record, which also appears on the slide PDX-10-15.

A. Yes.

"For the recommended application, as a short-term infusion over 30 minutes, no stability problems can be expected either, since there is a stability of nine hours for these bendamustine preparations at room temperature."

:45:14 Q. **What would a person of ordinary skill in the art in**
:45:17 **2005 understand from this teaching in Maas, Dr. Winter?**
:45:23 A. **He would understand that he is not to expect stability**
:45:27 **problems when he is going to use this drug, as it is**
:45:31 **recommended he should even have, as we call it, a safety**
:45:37 **margin above this, say, 30 minutes or however long it takes**
:45:42 **to administer that drug, because the difference between 30**
:45:46 **minutes and nine hours is significant in my eyes.**
:45:51 Q. **What type of solution did Maas focus on for her study**
:45:55 **that is reported in this paper?**
:45:56 A. **This was a solution where you dilute the Ribomustin**
:46:02 **product in an isotonic sodium chloride solution.**
:46:06 Q. **Would the degradation that Maas determined in sodium**
:46:10 **chloride or saline apply to solutions of water?**
:46:15 A. **In general, yes. But the degradation in sodium**
:46:19 **chloride is different than in pure water.**
:46:22 Q. **If we could please go back to PDX-10-13.**
:46:28 **Dr. Winter, in your opinion, why does the Gust**
:46:33 **reference not motivate a person of ordinary skill in the art**
:46:36 **to reformulate Ribomustin?**
:46:37 A. **Because Gust only focuses on bendamustine degradant.**
:46:45 **He characterizes that by chemical means. He does not**
:46:50 **provide degradant levels for this product as such. And he**
:46:55 **not at all addresses pre-lyophilization solutions. In fact,**
:47:01 **he makes reference to Maas and provides matter to identify**

:47:07 degradation products where it has been spoken about before.
:47:13 Q. If we could go to the next slide.
:47:17 Dr. Winter, in your opinion, why does the
:47:19 Ribomustin monograph not motivate a person of ordinary skill
:47:23 in the art in 2005 to engage in the redevelopment of
:47:27 Ribomustin?
:47:30 A. I see no information in the Ribomustin monograph that
:47:34 should motivate to do so because it provides instructions
:47:38 for clinical use. It states that a dry product, a
:47:45 lyophilisate as such has a two-year shelf life. It tells
:47:49 that it reconstitutes usually within five to ten minutes.
:47:55 And again, it does not address at all any pre-lyophilization
:47:59 solution or aspects of that manufacturing part.
:48:03 Q. Did any of the references that you reviewed in the
:48:06 course of your work in this litigation identify the solvent
:48:11 used in the pre-lyophilization solution for Ribomustin?
:48:15 A. No, nowhere did I see any such information.
:48:19 Q. Did any of the references that you reviewed in the
:48:21 course of this litigation describe the stability of the
:48:24 pre-lyophilization solution used for Ribomustin?
:48:28 A. No.
:48:29 Q. So based on the references that you have reviewed with
:48:33 regard to Ribomustin, would a person of ordinary skill in
:48:35 the art have had any reason to engage in the redevelopment
:48:38 or the development of a new lyophilized product of

:48:43 **bendamustine?**

:48:43 **THE COURT: Yes.**

:48:44 **MR. CWIK: Your Honor, that is the third leading question.**

:48:46 **THE COURT: That's fair.**

:48:46 **MR. MITROKOSTAS: I will withdraw it, Your Honor.**

:48:48 **BY MR. MITROKOSTAS:**

:48:50 Q. **Dr. Winter, in your opinion, was there a motivation for the person of ordinary skill in the art?**

:48:51 A. **No, I do not see such a motivation.**

:48:54 Q. **Now, do you recall Dr. Kwan and Dr. Kamat's testimony that a person of ordinary skill in the art would engage in the redevelopment of Ribomustin because of the fact that bendamustine was known to degrade in water?**

:48:56 A. **I recall that, yes.**

:48:58 Q. **Do you agree with them?**

:49:02 A. **No, I do not.**

:49:05 Q. **Why not?**

:49:08 A. **Because, as we have outlined before, the fact that a drug substance is sensitive to water or degrades in water is by no means a reason not to engage in such a lyophilized product.**

:49:11 Q. **And do you also recall Dr. Kamat and Dr. Kwan's testimony that a person of ordinary skill in the art would**

:49:13

:49:14

:49:15

:49:16

:49:22

:49:25

:49:30

:49:31

:49:36

have been motivated to reformulate Ribomustin in order to shorten the reconstitution time of that product?

A. I recall this, yes.

Q. Do you agree with them?

A. No, I do not.

Q. Why not?

A. Because this reconstitution time, in the context of how the drug is used, as we just heard in the context of the monograph, is absolutely applicable and not problematic.

Q. Have you seen any reports in the documents that you have reviewed about Ribomustin that the reconstitution time could take longer than the five to ten minutes stated on the product monograph?

A. I have not seen such documents before 2005. I have seen such documents in the course of preparation that were not available to the public that speak about longer reconstitution times.

Q. So in your opinion, would that have motivated -- would the fact that Ribomustin was later discovered to have a longer reconstitution time than five to ten minutes, would that have motivated a person of ordinary skill in the art in 2005 to reformulate Ribomustin?

A. No.

Q. Dr. Winter, if a person of ordinary skill in the art decided hypothetically in 2005 to reformulate Ribomustin,

:51:10 would that person have developed a lyophilized composition
:51:15 of bendamustine?
:51:20 A. This would have been one option besides others, yes.
:51:24 Q. What other types of formulations might that person of
:51:26 ordinary skill in the art have considered?
:51:29 A. A liquid formulation as well.
:51:51 Q. And why would that person of ordinary skill in the art
:51:56 have considered a liquid formulation of bendamustine?
:51:59 A. Because a liquid formulation from a general
:52:06 perspective is always the preferable pharmaceutical
:52:15 formulation for parenteral drugs.
:52:16 Q. Have you prepared a slide to describe why in your
:52:18 opinion a liquid formulation is preferable?
:52:21 A. I did so, yes.
:52:22 Q. All right. If we could have the next slide, please;
:52:25 which is 10-16.
:52:27 Dr. Winter, why in your opinion is a liquid
:52:30 formulation preferable to a lyophilized formulation?
:52:34 A. Yes. This is quite straightforward because the liquid
:52:39 formulation is more easy to handle and to use. There's no
:52:44 reconstitution step that are included or necessary, and the
:52:51 way to get there is much cheaper and faster than the way
:52:56 towards a lyophilized product.
:52:58 Q. And are there any disadvantages to a lyophilized
:53:01 formulation?

:53:01 A. **Yes, there are. They sort of evolved from that what I**
:53:08 **just said, that if you do have a two-piece at least product**
:53:13 **of a solid dosage form, the lyophilized product and a liquid**
:53:18 **which have to be mixed and handled and maybe put into a**
:53:23 **separate container. We do have extra handling steps with**
:53:28 **that. With that reconstitution step, you have a potential**
:53:32 **for error, for certain issues, including microbiological**
:53:37 **issues. And, of course, the way to the lyophilized**
:53:41 **products, as I said before, is more expensive and**
:53:44 **time-consuming.**
:53:45 Q. **Have you reviewed any references that discuss liquid**
:53:50 **formulations of bendamustine prior to 2005?**
:53:54 A. **I did, yes.**
:53:54 Q. **Do you recall what one of those references are?**
:53:59 A. **Yes. I think it is the so-called Olthoff reference.**
:54:09 **We I think have an excerpt on that.**
:54:10 Q. **Dr. Winter, if you could please direct your attention**
:54:13 **to JTX-55?**
:54:14 A. **Yes. This is what I mean.**
:54:16 Q. **All right. And do you do you recognize this**
:54:20 **document?**
:54:20 A. **Yes. This is the so-called Olthoff patent, and it**
:54:26 **describes a liquid form, a liquid pharmaceutical formulation**
:54:32 **for Bendamustine.**
:54:33 **And I took out a sentence here, the**

headline objective of the invention that reads, It is the objective of the invention to produce a stable and ready-to-use injection solution out of N-mustard compounds, avoiding the technical solution of a dry ampoule.

Q. Do you have an opinion, Dr. Winter, on what direction a person of ordinary skill in the art in 2005 would have been led based on the teachings of Olthoff?

A. Well, based on Olthoff, the person would have seriously considered whether a liquid dosage form would be an interesting alternative or improvement over the existing Ribomustin.

Q. Dr. Winter, let's now turn to your opinions on the validity of the claims 5 and 8 of the '190 patent, which is JTX-1 in your binder.

A. Yes.

Q. All right. And if we could have the next slide, please, 10-19.

And the claims, Dr. Winter, appear in column 34 of JTX-1? They're also on slide 10-9.

Dr. Winter, what is the subject matter of claims 5 and 8?

A. The subject matter of Claim 5 is describing a lyophilized pharmaceutical composition deriving from a solution that has a specific concentration of bendamustine hydrochloride of about 12 to 17 ml per ml. A specific

:56:24 **concentration for mannitol, 20 to 30 ml per ml, and a range**
:56:29 **of concentrations in volume, volume basis of tertiary butyl**
:56:37 **alcohol from 10 to 50 percent.**
:56:39 Q. **Now, do you agree with Drs. Kamat -- Dr. Kamat, that**
:56:43 **Claims 5 and 8 were obvious to a person of ordinary skill in**
:56:45 **the art in 2005?**
:56:47 A. **I do not agree.**
:56:48 Q. **Why not?**
:56:49 A. **Because I see no information in the prior art that**
:56:55 **should have led a POSA to an invention or a composition, as**
:57:03 **it is outlined here, outlined here in these claims.**
:57:10 Q. **And, in particular, what, for what reasons would a**
:57:13 **person of ordinary skill in the art not have found the**
:57:17 **claimed subject matter obvious?**
:57:18 A. **Well, there are several reasons, and we have them here**
:57:22 **on the screen. There's, first of all, the lack of**
:57:26 **motivation, as we saw. In fact, there is no problem with**
:57:32 **Ribomustin.**
:57:33 **Second, I see no reasonable expectation**
:57:36 **of success in using this particular TBA/water solvent**
:57:41 **system.**
:57:42 **Third, it is my opinion that extensive**
:57:47 **experimentation would have been needed to determine the**
:57:52 **concentrations of ingredients we just heard about in the**
:57:55 **claim.**

:57:56 **And, finally, there's limitation of 0.5 or less than 0.5 of the compound BM1EE was not inherent in the use of TBA/water solvent.**

:58:13 Q. **Now, Dr. Winter, since you already discussed the no motivation in the prior art, I want to focus your attention next to the use of TBA/water as a co-solvent system based on the prior art that Dr. Kamat described in his testimony. And he described a number of references, but I want to focus your attention on four main references for your testimony.**

:58:37 A. **Okay.**

:58:38 Q. **If we could --**

:58:40 **MR. CWIK: Your Honor, I would like to object to this line of testimony.**

:58:43 **Dr. Welton on Friday gave extensive testimony on solvents and how they are used in the pre-lyo solution. Any testimony Dr. Winter would give today on that same topic would be repetitive and duplicative and is just going to be make it an unnecessarily long day.**

:59:02 **MR. MITROKOSTAS: Your Honor, I apologize. I should have been made clear, I apologize, that Dr. Winter will not discussing the stability for the use of solvents or the stability of a pre-lyo solution, which is what Dr. Welton focused on.**

:59:13 **He is going to -- Dr. Winter will be discussing**

:59:13 **the other aspects of Teagarden that their experts testified**
:59:17 **about with respect to the use of solvents and how that could**
:59:19 **impact cake quality, reconstitution time.**
:59:22 **It's not duplicative testimony. We've separated**
:59:25 **out their testimony so that Dr. Welton could do the**
:59:27 **stability of the pre-lyo solution and Dr. Winter could focus**
:59:32 **on his expertise, which is all of these other factors that**
:59:35 **go into lyophilization.**
:59:38 **THE COURT: Yes?**
:59:38 **MR. CWIK: And, your Honor, Dr. Welton did**
:59:40 **discuss more the just the stability of using solvents in a**
:59:43 **pre-lyo solution. He talks about the pre-lyo solution as a**
:59:44 **whole and the use of solvents and what they did and what**
:59:48 **they did not do.**
:59:49 **So I understand Dr. Winter can talk about, you**
:59:51 **know, the lyophilization process and resulting cake and**
:59:55 **things like that, but we've already gone through the entire**
:59:59 **process of the pre-lyo solution and what the problems do to**
:00:00 **a pre-lyo solution.**
:00:00 **THE COURT: Well, counsel, both of you, I have**
:00:02 **not had the benefit of daily transcripts. Okay? So I don't**
:00:05 **know exactly. I have notes, okay, and I could go back and**
:00:08 **refer to my notes to try to discern whether you're right, or**
:00:13 **whether you're right.**
:00:15 **I'm not sure who is right, quite frankly. I**

:00:18 seem to recall that it was Dr. --
:00:26 MR. MITROKOSTAS: Dr. Welton.
:00:27 THE COURT: His discussion was somewhat limited
:00:31 in the fashion, but may have drifted, as you suggest.
:00:34 Go ahead, Mr. Cwik.
:00:36 MR. CWIK: Yes your Honor. I just wanted to
:00:38 raise that issue for you. We'll see where it goes.
:00:39 THE COURT: Well, it really does not present an
:00:41 evidentiary issue. It presents a practice issue for me and
:00:46 what is my practice, so I don't know that there's an
:00:48 evidentiary basis.
:00:49 MR. CWIK: Right.
:00:50 THE COURT: You made the objection. So it's my
:00:52 time to spend with you if I choose. And I'm going to
:00:56 listen. Okay?
:00:58 MR. MITROKOSTAS: Thank you, your Honor. And we
:00:59 have no intention of duplicating.
:01:01 THE COURT: I'm quite sure you don't.
:01:03 BY MR. MITROKOSTAS:
:01:04 Q. Dr. Winter, if you could please turn to DTX-999 in
:01:09 your binder.
:01:12 A. Yes, I am there.
:01:13 Q. And do you recognize this reference?
:01:20 A. Yes. It is the so-called Teagarden review.
:01:25 Q. Does Teagarden address bendamustine?

A. **No, not at all. It does not mention that.**

Q. **Does that have any significance to your opinion on whether a person of ordinary skill in the art would have utilized the teachings of Teagarden to make a lyophilized pharmaceutical product in 2005?**

A. **It has a very significant relevance to that opinion, yes.**

Q. **And --**

THE COURT: Just a second. Mr. Cwik, just to be fair, I didn't mean to suggest that the Court does not have access to daily transcripts in thinking about it. That would be just not true. Okay?

MR. CWIK: No, I --

THE COURT: As a service to my reporters because, of course, you guys are paying for it, I, know and they will provide it to me as well. So I just wouldn't have an inclination to sit down in the evening and read it, so that's -- I'm sorry.

BY MR. MITROKOSTAS:

Q. **Dr. Winter, what significance would a person of ordinary skill in the art place on the fact that Teagarden does not address bendamustine?**

A. **I think this significance derives from Teagarden's review itself, because he points out several times that this aspect is so complex that it has to be decided on a**

:02:44 case-by-case basis what happens if you enter into a
:02:49 complicated method of drying from solvent or co-solvent
:02:55 mixtures. And this I think tells us very clearly that the
:03:00 lack of information or teaching about bendamustine is highly
:03:05 relevant how I consider now this preference.
:03:09 Q. All right. If you could please turn, Dr. Winter, to
:03:12 DTX-999.002, which is internal Page 1 of Teagarden and
:03:22 appears on PDX-10-25.
:03:25 A. Yes, I'm there.
:03:26 Q. If you could please read the first sentence, Dr.
:03:29 Winter, as highlighted on there?
:03:30 A. Yes. It says, "However, the development scientist
:03:35 must be aware that use of these organic/water co-solvent
:03:40 systems can cause a multitude of problems."
:03:44 Q. And generally, what problems does Teagarden set forth
:03:47 with the use of organic solvents and lyophilization?
:03:49 A. Well, they are just following here in this
:03:52 paragraph, I don't want to repeat them all, but it's
:03:57 from toxicity concerns through flammability, of course,
:04:02 other technical aspects and so on. There's a multitude of
:04:05 these problems.
:04:06 Q. If you could now read the next highlighted sentence on
:04:10 PDX 10-25.
:04:11 A. Yes. "One should remember that successful sterile
:04:15 formulations should always employ an understanding of the

fundamental interrelationships between the formulation, the process, and the packaging. And I fully agree with that statement of Teagarden."

Q. And then the last sentence, which is highlighted on PDX-10-25.

A. Here he says, The advantages and disadvantages of their use must be carefully weighed before they are chosen to be used in the manufacture of a pharmaceutical product, especially one that is an injectable dosage form.

Q. Do you have an opinion as to what a person of ordinary skill in the art reading this discussion of organic solvents in Teagarden would have understood?

A. Yes. I have a very clear opinion on that, because it partly speaks for itself that you have to weigh, and I would say balance advantages, disadvantages. You have to carefully evaluate what you do there because it is interrelated and complicated.

Q. And if you could now turn, Dr. Winter, to Table 1 of Teagarden.

And I know this was also the subject of some testimony, and I'm not intending to duplicate what was --

A. Yes, I'm there.

Q. All right. Now, Dr. Winter, what's set forth in Table 1 of Teagarden?

A. Table 1 is a list of properties of organic solvents

:05:46 **evaluated in freeze driving. This is what it is.**
:05:50 Q. **And is this an exhaustive list of solvents that a**
:05:54 **person of ordinary skill in the art would have considered in**
:05:56 **2005?**
:05:57 A. **No, it is not an -- not an exhaustive list.**
:06:02 Q. **How do you know that?**
:06:06 A. **Very easy, because Teagarden itself -- and I think**
:06:13 **this is the paragraph just above this table in the, in the**
:06:19 **parentheses review, it says, A list of some of the solvents**
:06:23 **which have been tested in freeze-drying studies is provided**
:06:27 **in Table 1.**
:06:28 Q. **Now, does Table 1 identify the vapor pressure,**
:06:33 **freezing point, boiling point of a number of solvents?**
:06:36 A. **Yes, it does.**
:06:37 Q. **All right. And what would happen? I guess this vapor**
:06:42 **pressure, freezing point and boiling point that's set forth**
:06:46 **in Table 1, is that for a solvent on its own or in**
:06:50 **combination with other solvents?**
:06:52 A. **No, no. This is the -- this is for the solvent of its**
:06:58 **own. As you said, it's the pure solvent, and all these**
:07:04 **values would, of course, dramatically change if you mixed**
:07:09 **these solvents with what's most likely water.**
:07:13 Q. **Now, could the list of solvents in Table 1 and the**
:07:15 **other solvents that you say a person of ordinary skill in**
:07:18 **the art could have used, could they have been used in**

:07:20 combination with other co-solvents and mixtures?
:07:23 A. Yes, of course. They could be combined or mixed
:07:27 with water and they could also be combined with each
:07:31 other.
:07:32 Q. And approximately how many co-solvent systems would
:07:37 have been possible in 2005 for a person undertaking
:07:40 lyophilization, Doctor?
:07:41 A. Yes. That's theoretically an innumerate number
:07:46 because you can mix these solvents and co-solvents in many,
:07:50 many, many concentrations, and by that resulting in many
:07:56 co-solvent systems. You would use the term then.
:08:00 Q. Would a person of ordinary skill in the art be able to
:08:03 reasonably predict which of any of these co-solvent systems
:08:06 would work for bendamustine as of 2005?
:08:09 A. No.
:08:09 Q. Why not?
:08:10 A. Because I do not see a basis, and particularly not
:08:17 from the teaching of Teagarden just reviewed before to
:08:21 predict that was to select it up front.
:08:25 Q. Now, let's turn to another part of Teagarden, which is
:08:30 the first page, DTX-999-001.
:08:34 A. Yes.
:08:35 Q. Do you recall the testimony of defendants' experts
:08:43 that based on Teagarden's teaching on solubility, that a
:08:48 person of ordinary skill in the art would have selected TBA

:08:51 **as an organic co-solvent for bendamustine in 2005?**
:08:55 A. **I recall it, yes.**
:08:29 Q. **Do you agree with them?**
:08:35 A. **No, I do not.**
:08:35 Q. **Why not?**
:08:36 A. **Because this general idea, which is displayed here as a citation from Teagarden, that such nonaqueous solvent systems could be advantages by increasing solubility, does just not apply to bendamustine, because there is no such solubility problem.**
:09:01 Q. **How do you know that?**
:09:03 A. **I know that, for example, from Maas, from the literature we just made reference to a few minutes ago, and there is a citation from Maas, which is very clear and speaks for itself.**
:09:21 **"Bendamustine has good solubility in pure water."**
:09:24 Q. **Is that in DTX-577.001 or internal Page 1 of Maas, Dr. Winter, that you are reading from?**
:09:31 A. **This was a bit fast, but you were just reading this document identification.**
:09:36 **Yes, it is.**
:09:37 Q. **I am sorry. I will slow down.**
:09:41 **Dr. Winter, let's turn to another section in Teagarden, which discusses the freezing process. Dr.**
:09:53

:09:59 **Winter, what is the freezing process, just as background?**
:10:03 A. **The freezing process is the first significant step in**
:10:10 **freeze-drying, because you have frozen down the material,**
:10:15 **the solution, we have provided or prepared before.**
:10:19 **So then the interesting things are going to**
:10:24 **start, because we later want to dry from a frozen matter.**
:10:29 **And Teagarden spends more than two columns on the freezing**
:10:35 **process or on the effect of freezing by solvents and solvent**
:10:39 **mixtures, because here it really gets complicated. And I**
:10:45 **took out a reference from that part.**
:10:48 Q. **So if I could direct your attention, Dr. Winter, to**
:10:53 **Page 119, internal Page 119 of Teagarden, which appears on**
:10:59 **Slide 10-32. If you could read what Teagarden states here**
:11:03 **with respect to the freezing process and the use of organic**
:11:07 **co-solvents?**
:11:08 A. **He says, "Not surprisingly, the type and concentration**
:11:11 **of the organic solvent that is present affects the freezing**
:11:18 **characteristics of the solution prior to initiation of**
:11:22 **drying. The resulting frozen or semi-frozen solution**
:11:26 **significantly impacts the crystal habit of the ice, the**
:11:31 **drying rates, the collapse temperatures, the appearance of**
:11:34 **the dried cake, the surface area of the dried cake, and**
:11:38 **reconstitution properties, et cetera."**
:11:41 Q. **Do you have an opinion as to what a person of ordinary**
:11:43 **skill in the art would have understood from reading**

:11:48 **Teagarden's discussion of the use of co-solvents in the**
:11:53 **freezing characteristics or freezing process?**
:11:56 A. **This person would have understood that this part of**
:12:00 **the process already is extremely complicated, and this is**
:12:05 **just a citation we picked out. As I said, it goes on for**
:12:11 **two more pages.**
:12:13 **This is what a POSA would take home from this**
:12:18 **teaching of Teagarden.**
:12:19 Q. **Does the use of an organic co-solvent impact, would a**
:12:24 **person of ordinary skill in the art have understood that it**
:12:27 **could impact the freezing process for bendamustine in 2005?**
:12:32 A. **Of course, yes, they would have understood that.**
:12:36 Q. **Would the person of ordinary skill in the art have**
:12:38 **been able to predict what that impact would have been in the**
:12:41 **lyophilization of bendamustine in 2005?**
:12:44 A. **No, he would not have been.**
:12:45 Q. **Why not?**
:12:46 A. **Because, as I just said, the implications in general**
:12:50 **are unpredictable, complex, and even more would they be**
:12:58 **unpredictable if you now pick a certain compound and try to**
:13:02 **predict what should happen with this particular compound,**
:13:05 **maybe even in the presence of an excipient on top.**
:13:08 Q. **Let's now turn to the last section of Teagarden that**
:13:12 **you will be addressing in your testimony today, which is on**
:13:15 **Page DTX-999.0009.**

:13:23 **Dr. Winter, what does Teagarden state here in this section regarding the impact of solvents on reconstitution properties of a lyophilized product?**

:13:34 A. **He states, besides others, "The ability of the freeze-dried cake to readily reconstitute upon addition of an appropriate pharmaceutical solvent is dependent on several factors."**

:13:48 **Now he starts to go into these factors, and a bit later he then says, "Depending on the organic co-solvent selected and processing conditions used to freeze-dry, the product may or may not readily reconstitute. Therefore, one will need to evaluate this property on a case-by-case basis."**

:14:18 Q. **What would a person of ordinary skill in the art reading this part of Teagarden in 2005 have understood about the impact of co-solvents on reconstitution properties?**

:14:31 A. **He would have understood that it is again absolutely unpredictable. It may or may not help. It may even lead to a situation where the stuff is not readily reconstituting. The text speaks for itself. This is what the POSA would take home.**

:14:50 Q. **Dr. Winter, do you recall the testimony from defendants' experts that a person of ordinary skill in the art would select TBA as a co-solvent based on Teagarden's teachings regarding reconstitution time?**

:15:03 A. **Yes, I recall that.**
:15:03 Q. **Do you agree with them?**
:15:05 A. **No, I strongly disagree.**
:15:06 Q. **Why?**
:15:08 A. **Because we just heard that predictions are impossible. You have to take a case-by-case study. And it is no way so that Teagarden delivers a teaching that tells us that reconstitution would be better when you apply TBA, it even does not give one single example, except an example on sucrose, a sugar, without any drug in it.**
:15:44 Q. **Dr. Winter, based on Teagarden, would a person of ordinary skill in the art in 2005 have a reasonable expectation of success in improving Ribomustin through the use of a TBA-water co-solvent system?**
:15:58 A. **No, I do not think so.**
:16:00 Q. **What would the person of ordinary skill in the art have had to have done in 2005 in order to select an appropriate solvent system to lyophilize bendamustine?**
:16:13 A. **He would have had to enter into a significantly large set of experimentations to carry that out.**
:16:24 Q. **Let's turn to the next reference, Dr. Winter, which is the Ni reference that defendants' expert testified about. Again, I am going to limit your discussion of Ni to issues that have to do with lyophilization and not the stability of the pre-lyophilization solution or degradation.**

Ni, Dr. Winter, is JTX-79.

Do you recall defendants' experts' testimony that the Ni reference would have taught the person of ordinary skill in the art to use a TBA-water co-solvent system for bendamustine in 2005?

A. **I recall that, yes.**

Q. **Do you agree?**

A. **No, I do not.**

Q. **Why not?**

A. **Because the teaching of Ni is different. It does not teach the use of TBA-water co-solvent is applicable or obvious, for that particular matter, to formulate bendamustine.**

Q. **Does the Ni reference address bendamustine?**

A. **No, not at all. It addresses a drug called SarCNU.**

Q. **Does the fact that the Ni reference does not address bendamustine have any significance to your opinion?**

A. **Oh, yes, it has.**

Q. **What is that significance?**

A. **It is the significance, what we just learned before, that we have to apply case-by-case considerations and certain results we achieve for one drug cannot be transferred directly to others.**

Q. **If we could go to the next slide, please, 10-39.**

Dr. Winter, I want to direct your attention to

:18:12 **internal Page 44 of the Ni reference, under a section**
:18:17 **entitled Freeze-Drying Cake. Do you see that?**
:18:21 A. **Yes, I see it.**
:18:23 Q. **Does Ni describe what solvents she used in analyzing**
:18:29 **the properties of solvents on freeze-drying cake?**
:18:32 A. **Yes. She uses water, she uses different TBA-water**
:18:38 **mixtures, and then finally she used pure TBA.**
:18:42 Q. **And what would a person of ordinary skill in the art**
:18:45 **understand from this statement in Ni with regard to how TBA**
:18:49 **might affect the cake for SarCNU?**
:18:57 A. **I should surely read that: "No cake was formed when**
:19:01 **water was used to freeze-dry SarCNU. It was found that**
:19:07 **higher concentrations of TBA in TBA-water mixtures improved**
:19:11 **cake quality and the most uniform cake is produced from pure**
:19:16 **TBA."**
:19:17 **That for me is a clear teaching that for a very**
:19:20 **good cake use TBA.**
:19:24 Q. **Did Ni use any bulking agents in the compositions that**
:19:29 **she tested?**
:19:30 A. **No, she did not. We find that evidence in the**
:19:37 **materials and process section of this particular reference.**
:19:43 **It is already up on the screen.**
:19:45 Q. **Are you indicating internal Page 41 of the Ni**
:19:49 **reference?**
:19:50 A. **Yes. In fact, I do.**

Q. **If you could just read that sentence, Dr. Winter?**

A. **It says, "Solutions of SarCNU were prepared at a concentration of 5 milligrams per milliliter in TBA."**

And that also says that there was nothing else in there except SarCNU.

Q. **So did Ni use mannitol in her formulations?**

A. **No, not at all.**

Q. **Does the fact that Ni did not use mannitol in her formulations have any significance to your opinions on what a person of ordinary skill in the art would have understood from this reference?**

A. **Yes, it has, because adding mannitol would have changed the picture and made it, again, even more -- even less possible to predict from there to a different drug or different formulation task.**

Q. **Would a person of ordinary skill in the art in 2005 reading the Ni paper reasonably predict that they could achieve the same cake quality that Ni achieved with her compositions from a composition containing bendamustine and mannitol?**

MR. CWIK: Objection, Your Honor. Leading.

THE COURT: Try it again.

BY MR. MITROKOSTAS:

Q. **Dr. Winter, in your opinion, do the teachings of Ni apply to a situation where the person of ordinary skill in**

:21:22 **the art is lyophilizing bendamustine in mannitol?**

:21:25 A. **No, they do not apply.**

:21:26 Q. **Why not?**

:21:28 A. **Because we have two changes, one, first, a different**

:21:35 **drug, and second, an excipient which is here, in the one**

:21:38 **case, and not there in the other case.**

:21:41 Q. **Do excipients like mannitol have any impact on cake**

:21:45 **quality?**

:21:46 A. **Oh, yes, they have a dramatic impact on cake quality.**

:21:50 Q. **Can you provide a brief explanation of how?**

:21:54 A. **Yes. The cake, so to say -- Your Honor, excuse me, I**

:22:00 **use this term in the science on lyophilization all the**

:22:04 **time -- it is meant, the physical solid structure of the**

:22:09 **matter that is sort of left over when the solvent is gone.**

:22:13 **This cake structure or this cake consists, largely consists**

:22:20 **of that which is left over, which is the drug and an**

:22:24 **excipient. Therefore, it is quite clear that an excipient,**

:22:28 **its type, and its amount dramatically affect the cake**

:22:33 **structure.**

:22:34 Q. **Dr. Winter, finally, do you recall Dr. Kamat's**

:22:39 **testimony relating to two other TBA references --**

:22:43 A. **Sorry. I was just a second not concentrating. Could**

:22:45 **you repeat?**

:22:46 Q. **Of course. Do you recall Dr. Kamat's testimony**

:22:49 **relating to two other TBA references, Lyondell and Baldi?**

:22:54 A. **Yes.**

:22:55 Q. **Do you agree with Dr. Kamat that these references would have taught a person of ordinary skill in the art in 2005 to use TBA in a pre-lyophilization solution with bendamustine?**

:23:06 A. **I disagree.**

:23:07 Q. **Have you prepared a slide to summarize your opinions on that issue?**

:23:12 A. **Yes, I did.**

:23:14 Q. **If we could please go to PDX-10-44.**

:23:20 **Dr. Winter, what were the key teachings to a person of ordinary skill in the art reading Baldi and Lyondell in 2005?**

:23:28 A. **First going Baldi, Baldi used gentamicin and mannitol and made lyophilized cakes out of that. And he teaches us, in that background, that lyophilization may require multiple variable analyses. And he proposed that one should potentially use computer software like MODI, which is a statistical experimental analysis software.**

:24:00 Q. **And what about Lyondell?**

:24:02 A. **Lyondell, it's not a publication. It's a brochure. It's a color brochure from a company that is selling TBA. And it compiles information from all of the literature about the potential use of TBA. It's a non-peer-reviewed compilation.**

:24:27 Q. **So, Dr. Winter, do you have an opinion as to whether a**
:24:30 **person of ordinary skill in the art seeking to improve**
:24:33 **Ribomustin would have selected TBA as the co-solvent based**
:24:37 **on the references that we have reviewed in your testimony?**
:24:39 A. **I have an opinion. And this opinion is he would not**
:24:43 **have done so.**
:24:46 Q. **Let's now take a look, Dr. Winter, back at Claim 5 of**
:24:50 **the '190 patent, which is on PDX-10-45. Dr. Winter, do you**
:25:01 **recall Dr. Kamat's testimony that the concentrations claimed**
:25:04 **in Claim 5 would have been obvious to a person of ordinary**
:25:08 **skill in the art?**
:25:09 A. **I recall this.**
:25:10 Q. **Do you agree?**
:25:11 A. **No, I do not agree.**
:25:12 Q. **Why not?**
:25:14 A. **Because I see no information from the prior art how to**
:25:19 **end up with that composition and concentrations. And I can**
:25:27 **only repeat, to end up at these concentrations and**
:25:31 **compositions, you have to go through experiments. You have**
:25:36 **to go through experiments.**
:25:42 Q. **And did the prior art disclose the concentration of**
:26:04 **bendamustine in Ribomustin's pre-lyophilization solution?**
:26:08 A. **No, it did not.**
:26:10 Q. **Without knowing that information, how would a person**
:26:14 **of ordinary skill in the art have been able to determine the**

:26:18 **appropriate concentration of bendamustine in a**
:26:21 **pre-lyophilization solution if they wanted to do that in**
:26:24 **2005?**
:26:25 A. **By experimentation.**
:26:26 Q. **And what about mannitol? Did the prior art on**
:26:33 **Ribomustin describe the concentration of mannitol in the**
:26:37 **pre-lyophilization solution for bendamustine?**
:26:40 A. **No, it did not describe the concentration.**
:26:44 Q. **And without knowing that information, how would a**
:26:47 **person of ordinary skill in the art trying to determine the**
:26:51 **appropriate concentration of mannitol in a**
:26:53 **pre-lyophilization solution of bendamustine have made that**
:26:58 **determination?**
:26:59 A. **Well, they would experimentally have tried it out and**
:27:07 **find a good solution that takes into an improved product.**
:27:11 Q. **And could the selection of a particular concentration**
:27:14 **of mannitol have any impact on the particular concentration**
:27:20 **that is used in the pre-lyophilization solution for the**
:27:23 **API?**
:27:25 A. **Yes, it could have such an implication or an effect,**
:27:28 **yes.**
:27:29 Q. **What are the potential impacts that the person of**
:27:30 **ordinary skill in the art would have understood in 2005?**
:27:33 A. **That the amount of mannitol would, as we heard**
:27:41 **earlier, affect the cake quality later, and that, of course,**

goes along with the amount of API as well. You have to consider that from the beginning.

Q. Let's turn now to the concentration of TBA that's claimed in Claim 5.

In your opinion, do you have an opinion as to whether a person of ordinary skill in the art would have been motivated to select 10 to 50 percent TBA as the co-solvent in the pre-lyophilization solution?

A. Yes, I have an opinion on that.

Q. All right. And what's your opinion?

A. My opinion is that this, there is no clear teaching from the prior art to an opposite selected concentration.

Q. Now, did you recall the testimony of Dr. Kamat, that the ranges of TBA used in the Teagarden reference would have motivated a person of ordinary skill in the art to come up with that concentration of TBA that's claimed in Claim 5?

A. I recall this, yes.

Q. Do you agree with him?

A. I do not.

Q. Why not?

A. Because we went through this reference and teaching in the prior art, and I have not seen information that would lead me towards that selection.

Q. If a person of ordinary skill in the art had decided

:29:09 **to use TBA as a co-solvent in 2005, how would they be able**
:29:14 **to select the appropriate concentration of TBA to use in a**
:29:19 **pre-lyophilization solution for bendamustine?**
:29:23 A. **They would have taken the experimental approach and**
:29:26 **selected it in the context of the API and the excipient in**
:29:30 **the solution and then find the preferred, the preferred**
:29:37 **concentration.**
:29:37 Q. **And prior to that experimentation, would they have**
:29:40 **been able to reasonably predict which particular**
:29:43 **concentration of TBA would have improved Ribomustin?**
:29:48 A. **No.**
:29:49 Q. **Why not?**
:29:49 A. **Because there is no basis for such a prediction.**
:29:57 Q. **If the person of ordinary skill in the art had engaged**
:30:01 **in this experimentation that we've been discussing with TBA,**
:30:06 **do you have an opinion as to whether he would have**
:30:08 **necessarily identified the particular concentrations that**
:30:12 **are claimed in Claim 5?**
:30:13 A. **Yes. My opinion is that he would not have necessarily**
:30:21 **ended up taking these concentrations.**
:30:24 Q. **And prior to experimenting with TBA, would the**
:30:30 **person of ordinary skill in the art have been able to**
:30:32 **reasonably predict if TBA would be able to improve**
:30:35 **Ribomustin at all?**
:30:36 A. **Could you just repeat the question so I'm sure that I**

get it correct?
Q. Yes. So if the person of ordinary skill in the art was seeking to improve Ribomustin --
A. Right.
Q. -- would they have been able to reasonably predict the impact of TBA and the pre-lyophilization on that endeavor?
A. No, no. They would not have been able to do so.
Q. Let's now take a look at Claim 8 of the '190 patent.
Dr. Winter, what's claimed in Claim 8 of the '190 patent?
A. Claim 8? So it's based on Claim 5, and that's one more particular limit that is, that is a pharmaceutic composition does not contain more than 0.5 percent of bendamustine ethylester.
Q. Do you understand that bendamustine ethylester is sometimes referred to as BM1EE?
A. Yes, I understand that.
Q. Do you recall Dr. Kamat's testimony that a composition with that amount of BM1EE, or bendamustine ethylester less than 0.5 percent would have been obvious because it would have been the inherent result of using TBA in the bulk solution with bendamustine?
A. I recall his testimony, yes.
Q. Do you agree with him?

:32:13 A. **No, I do not.**

:32:14 Q. **Why not?**

:32:14 A. **Because I do not see a correlation between the use of TBA and that result or that limit of bendamustine ethylester.**

:32:25 Q. **Did the prior art teach the amount of bendamustine ethylester that existed in the Ribomustin product?**

:32:29 A. **No, it did not.**

:32:34 Q. **And what about the amount of bendamustine ethylester in the API that was used to make Ribomustin? Was that disclosed in the prior art?**

:32:35 A. **No, I have not seen such disclosed anywhere.**

:32:46 Q. **And have you seen any references that describe the bendamustine ethylester in Ribomustin?**

:32:50 A. **I have seen references that talk about this particular compound, yes.**

:32:58 Q. **And do you recall one of those references?**

:33:05 A. **Yes. I think it was Gust.**

:33:08 Q. **All right. If we could go to the Gust reference, which is DTX-149, please.**

:33:13 **If you could direct your attention to that reference, Dr. Winter.**

:33:22 A. **Yes, I'm there.**

:33:24 Q. **And I want to direct your attention to internal Page 299. What's described here on Page 299 of the Gust**

:33:25

:33:27

:33:33

:33:37 **reference?**
:33:38 A. **What is described here and it is on the screen is the**
:33:47 **synthesis of this, of this compound, so I should explain**
:33:52 **that Gust wanted to synthesize that as a reference sample**
:33:59 **for analytical purposes, and this is the way.**
:34:05 Q. **And what were the conditions that Gust employed to**
:34:08 **synthesize the bendamustine ethylester?**
:34:11 A. **I just read the first sentence. It's quite short. It**
:34:16 **takes bendamustine, a certain amount. This was dissolved in**
:34:22 **the volume of ethanol and then treated with gaseous**
:34:27 **hydrochloric acid for 20 minutes, then stirred and later**
:34:32 **evaporated and crystallized.**
:34:34 Q. **How do the conditions that Gust describes here in this**
:34:38 **paper -- have you performed a comparison as to the**
:34:41 **conditions that Gust describes in his paper for making**
:34:46 **bendamustine ethylester with the typical conditions for**
:34:48 **lyophilization?**
:34:49 A. **Yes. And I say they have nothing to do with each**
:34:54 **other because these conditions here are, I would call them**
:34:59 **very harsh as using gaseous hydrochloric acid for**
:35:06 **20 minutes, it's really a harsh chemical condition.**
:35:09 Q. **Now, does Gust describe the formation of bendamustine**
:35:13 **ethylester in any other way?**
:35:15 A. **Yes. In the context of the synthesis, he comes to**
:35:22 **this compound as well.**

:35:23 Q. **And so if you direct your attention, Dr. Winter, to**
:35:27 **Page 293 of Gust, what does Gust describe here with respect**
:35:32 **to the bendamustine ethylester in the synthesis of**
:35:37 **bendamustine?**
:35:38 A. **First, what we see as bendamustine in the left lower**
:35:45 **corner, and to the right, degradation product, and what**
:35:49 **comes from the left upper corner is the way of the**
:35:54 **synthesis. And you do see that this compound we are just**
:35:58 **talking about, which is highlighted in yellow, is a**
:36:01 **precursor of bendamustine.**
:36:03 Q. **And what is the name of the compound that's**
:36:07 **highlighted in yellow that you are referring to?**
:36:08 A. **This is this -- here it is called dichloroester. This**
:36:15 **is the compound we just discussed in B1EE.**
:36:19 Q. **So what is Gust teaching the person of ordinary skill**
:36:21 **in the art with respect to the formulation of bendamustine**
:36:25 **ethylester during the synthesis of bendamustine?**
:36:27 A. **That it is a precursor, and therefore it could be**
:36:34 **there as a byproduct of bendamustine as well.**
:36:37 Q. **Would a person of ordinary skill in the art in 2005**
:36:43 **have any expectation of obtaining less than 0.5 percent**
:36:49 **bendamustine ethylester, if they used a pre-lyophilization**
:36:54 **solution using TBA?**
:36:57 A. **No, not at all. I do not see a basis for this**
:37:00 **assumption or expectation.**

:37:02 Q. **Dr. Winter, to conclude, were the formulations that**
:37:08 **are claimed in Claims 5 and 8 of the '190 patent obvious to**
:37:14 **a person of ordinary skill in the art in 2005?**
:37:16 A. **No, they were not obvious.**
:37:19 Q. **Let's now turn to the next patent.**
:37:23 **THE COURT: Since you're changing subjects,**
:37:24 **let's take a break.**
:37:25 **(Short recess taken.)**
:59:20 **THE COURT: Please take your seats. Doctor?**
:59:22 **Continue.**
:59:27 **MR. MITROKOSTAS: Thank you, your Honor.**
:59:28 **BY MR. MITROKOSTAS:**
:59:30 Q. **Dr. Winter, I'd like now to turn the focus on your**
:59:33 **opinions on validity of the '863 patent, and if we go to the**
:59:37 **next slide, please, PDX-10-52.**
:59:41 **Dr. Winter, what's claimed in the, in Claim 1 of**
:59:44 **the '863 patent?**
:59:45 A. **Here it's claimed a lyophilized preparation with API,**
:59:56 **mannitol, and a trace amount of TBA, and a very clearly**
:00:01 **defined ratio and weight of the bendamustine to mannitol,**
:00:06 **which is 15.25.5.**
:00:10 Q. **Do you have an opinion whether Claim 1 of the '863**
:00:13 **patent would have been obvious to a person of ordinary skill**
:00:15 **in the art in 2005?**
:00:16 A. **Yes. My opinion is it is not obvious.**

:00:20 Q. **Can you please explain why?**
:00:22 A. **Again, the reasons that applied to the previous patent**
:00:32 **applies here. There's no motivation, or there was no**
:00:36 **motivation in the prior art to reformulate Ribomustin, and**
:00:41 **there was no reasonable expectation of success to arrive**
:00:44 **there by using TBA/water solvent. But now there is more**
:00:50 **particular reason to apply to this patent claim, which is,**
:00:55 **in fact, that there is no motivation to increase the**
:01:00 **proportion of mannitol relative to bendamustine**
:01:03 **hydrochloride as it has been set out in this claim.**
:01:08 Q. **And have you compared the ratio of bendamustine to**
:01:15 **mannitol in the claim with the ratio of bendamustine to**
:01:19 **mannitol in the finished Ribomustin product?**
:01:22 A. **Yes, I did.**
:01:23 Q. **All right. Have you prepared a slide to --**
:01:26 A. **Yes. There it is.**
:01:28 Q. **All right. So, Dr. Winter, how does the ratio of the**
:01:35 **bendamustine to mannitol in Claim 1 of the '863 patent**
:01:39 **compare with the ratio of the bendamustine to mannitol in**
:01:43 **Ribomustin?**
:01:43 A. **Well, it compares very clearly, and so far that now**
:01:49 **the ratio API to mannitol is moved from 1 to 1.2 to 1 to**
:01:56 **1.7. In other words, the amount of mannitol is relevant.**
:02:01 **The amount of mannitol has increased, about 42 percent**
:02:06 **increase.**

Q. **Could increasing the amount of mannitol by 42 percent compared to Ribomustin have an impact on the lyophilized bendamustine product in your opinion?**

A. **Yes, it would most likely have such an impact.**

Q. **Okay. And in what ways could in increasing the amount of mannitol impact potentially the lyophilized bendamustine product?**

A. **We have seen these factors before. It is a cake structure. It is stability. It's a solution, and all of those factors we have seen in the chart at the beginning of our conversation.**

Q. **Would a person of ordinary skill in the art be able to reasonably predict how these factors would be affected by such a change in mannitol without experimentation?**

A. **No.**

Q. **So what would the person of ordinary skill in the art have had to have done in order to determine the appropriate amount of are mannitol to bendamustine for a lyophilized product in 2005?**

A. **You have to carry out significant amount of experimentation to potentially end up with these results.**

Q. **And while we're addressing this ratio of API to mannitol in the '863 patent, I want to direct your attention as well to two references that Dr. Kwan identified as confirming his opinion in the '756 patent, which has the**

:03:39 **same ratio, if that's all right, Dr. Winter?**
:03:42 A. **Yes, that's fine.**
:03:43 Q. **All right. Now, do you recall the testimony of Dr. Kwan that the Alexander, the Alexander patent and the Sauerbier patent confirmed his opinion that the claimed ratio of 15 to 25.5 would have been obvious in 2005?**
:04:00 A. **Yes, I recall this very well.**
:04:02 Q. **Do you agree with him?**
:04:04 A. **No.**
:04:05 Q. **Have you reviewed those references?**
:04:07 A. **I have reviewed his references, yes.**
:04:09 Q. **If you could please turn to DTX-349, which is the Alexander reference. And I want to direct your attention, Dr. Winter, to column 12, lines 46 to 59.**
:04:24 A. **Yes, I'm there.**
:04:25 Q. **All right. And does the Alexander patent address bendamustine?**
:04:29 A. **No. The Alexander patent is about cyclophosphamide.**
:04:36 Q. **What is the Alexander patent described here in column 12, lines 46 to 59?**
:04:44 A. **The patent describes compositions, solid compositions, freeze-dried compositions consisting of the drug cyclophosphamide, small amounts of water and mannitol. And we can take ratios for API and mannitol from these numbers, and then we would see that in a less preferred description,**

:05:18 **we see a rather large range, from 1 to 1.5 to 1 to 4.2 ratio**
:05:28 **API versus mannitol.**
:05:30 Q. **I'm sorry. What was the first ratio you mentioned in**
:05:32 **that range?**
:05:33 A. **1 to 0.5.**
:05:35 Q. **Okay.**
:05:36 A. **Did I misread that?**
:05:38 Q. **I may not have heard you.**
:05:39 A. **I'm sorry. 1 to 0.5.**
:05:42 Q. **And what is the magnitude of the difference in the**
:05:47 **range of API to mannitol ratio described here in the**
:05:53 **Alexander patent, Dr. Winter?**
:05:55 A. **You mean between the lowest and the highest?**
:06:00 Q. **Yes.**
:06:00 A. **That is about 8-fold range.**
:06:03 Q. **And have you also considered whether Alexander's**
:06:07 **teaching with respect to a most preferred composition in**
:06:10 **this patent?**
:06:11 A. **Yes, I did, and it's on the same page and, in fact, on**
:06:15 **the same paragraph two lines down. And the most preferred**
:06:20 **composition is that advance about 55 percent**
:06:24 **cyclophosphamide, 44 percent mannitol. And the math here,**
:06:31 **did the math here, and that ratio we come up with is 1 to**
:06:37 **0.75 API to mannitol.**
:06:41 Q. **All right. So in the most preferred ratio of the**

:06:43 **Alexander patent, is there more or less API than mannitol,**
:06:47 **Dr. Winter?**
:06:47 A. **It's just -- it's more API than mannitol.**
:06:04 Q. **Let's now turn to the Sauerbier patent, which is**
:06:38 **DTX-348. If you could please turn to that reference in your**
:06:43 **binder.**
:06:45 A. **What number?**
:06:46 Q. **DTX-348, please.**
:06:50 A. **Yes.**
:06:51 Q. **I want to direct your attention to Column 3, Line 26**
:06:55 **to 33?**
:06:59 A. **Yes.**
:07:00 Q. **What does the Sauerbier patent describe here in Column**
:07:05 **3, Lines 26 to 33, Dr. Winter?**
:07:08 A. **Here we do have a teaching about relative amounts of**
:07:14 **hexitol, which is another word for a group of alcohols that**
:07:19 **encompass mannitol, and ifosfamide, is the drug that is**
:07:26 **considered in Sauerbier. And in this case, we have**
:07:30 **highlighted here this excerpt, the amount may be from 0.1 to**
:07:39 **17.**
:07:42 **Again, this calculation is in the same order**
:07:45 **that reads it is one part API and 0.1 to the other extreme,**
:07:53 **one part to 17 parts of hexitol.**
:07:58 Q. **Can you remind us, what is hexitol?**
:08:02 A. **Hexitol, that is a choice, a different word for**

mannitol.

Q. And what is the difference between the ratio that has the least amount of hexitol compared to API as opposed to the ratio in the Alexander patent that has the most amount of hexitol in relationship to API?

A. It's a huge range. It's 174.

I think you misspoke. You meant Sauerbier.

Q. Sauerbier. Thank you, Dr. Winter.

Dr. Winter, is there an "in particular" composition that is described here in the Sauerbier patent?

A. Yes. It is. Down the line here in the same sentence, they call it "in particular," which I understand is to say most preferred or very well preferred. It is 0.6 to 0.8 parts by way of the hexitol.

Q. And so, Dr. Winter, in the "in particular" composition that is described here in the Sauerbier patent, is there more or less API than there is hexitol?

A. There is more API than hexitol.

Q. Have you compared the most preferred composition in Alexander and the "in particular" composition from Sauerbier with the Ribomustin product of the claimed invention?

A. Yes, I did so, to get a little more structure. There is many numbers. I prepared a slide.

Q. Turning now to PDX-10-61, can you please explain what you have depicted on this slide, Dr. Winter?

:09:48 A. **Yes. I made a scale, on the x axis, which displays**
:09:58 **the ratio between API to mannitol. Then I put these ratios**
:10:05 **we find in these different patents or products in relation**
:10:10 **to this scale on the left side. And I start here with**
:10:13 **Ribomustin, which is the older product, and the number we**
:10:18 **have seen before is 1 to 1.2. This is the ratio of API to**
:10:24 **mannitol.**
:10:24 Q. **Did you also compare the ratio of Ribomustin to the**
:10:29 **claimed invention?**
:10:31 A. **Yes. Here it is. So the claimed invention is on the**
:10:38 **scale above, it's 1 to 1.7. Again, what is meant is the**
:10:44 **ratio API to mannitol.**
:10:45 Q. **What does that mean in terms of how much more or less**
:10:48 **mannitol there is in the claimed invention as opposed to**
:10:51 **Ribomustin?**
:10:52 A. **That means we went up to 42 percent, putting more**
:10:59 **mannitol in the formulation in relation to API.**
:11:02 Q. **Did you also compare these two ratios with the**
:11:04 **preferred embodiments from Sauerbier and Alexander?**
:11:07 A. **Sure, I did. And here it is. This is, on the left,**
:11:11 **the lower side, Alexander, the most preferred number we have**
:11:16 **seen, and the right side, Sauerbier gives us a most**
:11:21 **preferred range. It is depicted in relation to the scale on**
:11:25 **the left side, and I think it is quite clear what the**
:11:32 **precision on this scale tells us, that most preferred,**

:11:36 **through the teaching of this reference, is going in an**
:11:40 **opposite direction than the inventors went when**
:11:44 **reformulating Ribomustin.**
:11:45 Q. **So in your opinion, would a person of ordinary skill**
:11:48 **in the art in 2005 reading Alexander and Sauerbier have had**
:11:54 **any reason to increase the amount of mannitol in Ribomustin?**
:11:59 A. **Not at all.**
:12:00 Q. **Did either Sauerbier or Alexander use TBA as a**
:12:05 **co-solvent?**
:12:06 A. **No, none of them used TBA.**
:12:08 Q. **Is that significant at all to your opinion?**
:12:12 A. **This is significant to my opinion, as we discussed the**
:12:18 **use of TBA in the context of why we are here, and it is of**
:12:25 **utmost significance as the drug molecules used in Alexander**
:12:32 **and Sauerbier are similar to bendamustine and have not been**
:12:37 **freeze-dried from the co-solvent system including TBA.**
:12:41 Q. **Now, do you also recall Dr. Kwan's testimony that due**
:12:48 **to the use of TBA increasing the porosity of a lyophilized**
:12:53 **cake, a person of ordinary skill in the art would increase**
:12:55 **the amount of mannitol?**
:12:57 A. **I read that, yes.**
:12:58 Q. **Do you agree with him?**
:12:59 A. **I do not agree.**
:13:00 Q. **Why do you disagree with him?**
:13:04 A. **Because I have not seen such a teaching in the**

literature, in the available literature's state of the art that would motivate me or someone to do this, to now add mannitol in the course of what you just described. There is no reason to do so.

Q. Would a person of ordinary skill in the art have had any reason to select the specific ratio of 15 to 25.5 claimed in the '863 patent based on the prior art?

A. No. I see no such reason based on the prior art.

Q. And in your opinion, how would the person of ordinary skill in the art, if they were able to arrive at that ratio, how would they have gotten there? What would they have needed to do?

A. I think they might have arrived there by doing experimentation and analysis of their experimental data.

Q. Is that experimentation routine, in your opinion?

A. No, it is not.

Q. Why not?

A. From the beginning, it's not routine because we do have here a dangerous drug, first of all, I have to say. Even the handling of that drug is complicated and all but routine.

Second, we do have lyophilization processes, maybe including TBA, which is not routine at all.

And third of all, we have seen that we move into directions that practically move away from that which we

have been taught from the literature.

And fourth of all, this type of experiment is rather high-level pharmaceutical development work, which is not routine.

Q. So, in your opinion, Dr. Winter, is Claim 1 of the '863 patent, would it have been obvious to a person of ordinary skill in the art in 2005?

A. No, it would not have been obvious.

Q. Let's now turn to the next patent that you analyzed, which is the '756 patent.

Dr. Winter, what is claimed in the '756 patent, Claims 1 and 4?

A. Yes. Just give me a second.

What is claimed, this time, is a reconstituted solution of bendamustine and mannitol, where now the ratio is the one we have seen before. And now we have a concentration given which is 100 milligrams per 20 milliliters in this reconstituted solution.

Shall I go on for Claim 4?

Q. Yes, please.

A. In Claim 4, we do have a concentration of solution like that. Now, it is clearly expressed that it is in a 20-milliliter vial, and also the amount of bendamustine and mannitol are now expressed in masses, whereas the ratio from the one to the other remains on the value we have seen above

in Claim 1.

Q. Do you recall Dr. Kwan's testimony that these claims were obvious to a person of ordinarily skill in the art in 2005?

A. I recall that.

Q. Do you agree with him?

A. No, I do not.

Q. Why not?

A. Because -- and I want to go fast here -- we have seen some reasons for nonobviousness before that apply here as well. But there is now some more aspects to be taken into account, and I would like to go to the first one, which is in bold letters.

There was no motivation to reduce the reconstitution diluent volume relative to Ribomustin, in other words, to make it more concentrated.

And what goes along with that in the same direction is that it was also not obvious now to reduce the vial size relative to Ribomustin.

Q. Is there any other reason, Dr. Winter, in your opinion, that Claims 1 and 4 of the '756 were not obvious?

A. Yes. The last point is that if you do so, you have to go there by experimentation to find out whether now these combined many steps towards that, whether that would improve product.

:17:51 Q. **In addition to requiring a ratio of bendamustine**
:17:55 **hydrochloride to mannitol of 15 to 25.5, does Claim 1**
:17:59 **require a particular concentration of bendamustine in the**
:18:01 **reconstituted solution?**
:18:03 A. **Yes, it does.**
:18:04 Q. **What is that concentration?**
:18:04 A. **This concentration is 100 milligrams to 20**
:18:10 **milliliters. We can express that in other numbers. I**
:18:16 **thought I had prepared, there is a slide on that, these**
:18:22 **numbers, to make it more easy to follow.**
:18:25 Q. **Have you compared the concentration of bendamustine in**
:18:28 **the reconstituted solution of the '756 patent with**
:18:33 **Ribomustin?**
:18:35 A. **Yes, I did, sir.**
:18:36 Q. **And I think you were referencing Slide PDX-10-65. Is**
:18:43 **that your comparison that you have done?**
:18:45 A. **That is exactly the comparison. Sorry for being fast.**
:18:49 **But I just was looking for this concentration number. And I**
:18:54 **am going to explain it very shortly.**
:18:56 **Here we have on the left side Ribomustin,**
:19:00 **according to the information that is outlined in the**
:19:02 **so-called Ribomustin monograph, and that leads to a final**
:19:09 **concentration of 2.5 milligrams per milliliter. It is easy**
:19:13 **to calculate from 100 divided by 40, on the right-hand side,**
:19:18 **it is now the claimed formulation, where we take information**

from Claim 1 and do the math, and have 5 milligrams per milliliter. Which it is easy to see the double concentration.

Q. What does it mean in terms of the amount of diluent volume change between Ribomustin in the claim by the fact that the concentration of bendamustine has doubled?

A. Yes. It's again to be seen here on the slide as well, the diluent volume has been reduced to half, from 40 to 20.

Q. Do you agree with Dr. Kwan that doubling the concentration of bendamustine in the reconstituted solution or reducing the volume of diluent in half would have been obvious to a person of ordinary skill in the art in 2005?

A. I disagree with that.

Q. Can you please explain why?

A. Yes. First of all, I see no reason, first of all, to go into that direction. And second, I think we have a situation where we increase the amount of mannitol, and we put in more material in the same container, and despite that going down with the volume we offered to dissolve that is counterintuitive. It is a nonobvious step.

Q. Why would it be counterintuitive, in your opinion?

A. Because offering less volume would most likely reduce the dissolution speed. It would increase the reconstitution time.

Q. Now, have you prepared a slide presentation to explain

your opinions on what potential impact reducing the volume could have on the reconstitution time of Ribomustin?

A. Yes, I did prepare a few slides. And may I direct your attention to just outline the concept?

The situation we do have when we reconstitute something, we can keep it general, is the dissolution of solid matter in liquids. And when we do so, we speak in science about sink conditions when we offer plenty, a large volume of the solvent, and then the matter can distribute or dissolve easily.

And then we can consider a different situation where we only offer very limited amount of solvent. And then the material dissolves as well when it's still below the equilibrium solubility threshold, but a consequence of offering less and more solvent as displayed on the next slide I consider, which is basic thermodynamics.

For sink conditions, now the upper half of the slide, you have a part unhindered dissolution, and when offer a very limited amount of solvent, this you see on the right lower corner, this dissolution or in the context.

Now we come to the context of the matter we discussed here. The reconstitution time will be prolonged. This is basic thermodynamics which applied for all solids and all solvents.

Q. And then the slide to which you were just referring at

:23:31 **the end is PDX-10-68; is that right?**

:23:34 A. **That's correct.**

:23:35 Q. **All right. Now, would the principles of sink conditions have been something that a person of ordinary skill in the art would have considered in the context of developing an improvement to Ribomustin if they were to do so?**

:23:49 A. **Yes, it would have been applicable to that as well.**

:23:53 Q. **And have you analyzed how the principle of sink conditions and dissolution and reconstitution time might impact the improvement over Ribomustin if someone was trying to do that?**

:24:05 A. **Yes, I have considered that, and I would now come back to the, our product or inventions, but stay with the same realization.**

:24:16 **Now we see the amount. We know it's numbers of 100 milligrams of bendamustine displayed here as the red balls, and we offer a certain volume. This volume is well-known. It's the Ribomustin 40 ml of volume water. And we do the solid in a certain dissolution.**

:24:38 **But now what the inventors have done is offering the half volume, which is displayed here. And we, by that, go into a direction which is from a thermodynamic basis, a step into the wrong direction. So we put it out in the direction that would theoretically lead to a slower**

dissolution which in our context is equivalent to reconstitution.

Q. And so what would a slower dissolution mean as far as reconstitution time, Dr. Winter?

A. Longer time. Longer reconstitution time.

Q. And would moving further away from sink conditions have been an important consideration to a person of ordinary skill in the art in 2005?

A. I think so, yes. I agree, yes, it would.

Q. Now, you mentioned before that there was another element that was potentially involved in this analysis with respect to sink conditions that's claimed in the claims of the '756 patent.

A. Oh, yes. There is the excipient as well. We have left that out so far to make it not too complicated in the first place, but I have added it here.

And it's very bad to see on the big screen, so I ask your Honor to look on your computer screen where we do have our mannitol added in dark purple circles. And we do have the same situation as before, but now it's made clear it's not just the bendamustine in there. It's also the mannitol that has to dissolve. They both dissolve together in this volume we offer.

And now the inventors take what we already heard. They do two things in one step. They reduce the

:26:37 **volume on the right side, and on the left side they increase**
:26:41 **the amount of mannitol from 120 to 170 mg per ml. And now**
:26:48 **as good as let's say the graphic can display that, we do**
:26:53 **have a situation that is very crowded and would**
:26:57 **thermodynamically very clearly lead to an expectation that**
:27:02 **dissolution had further slowed down. This is the message of**
:27:06 **this visualization I tried to provide you with.**
:27:12 Q. **And the two slides that you reference now that**
:27:13 **discuss mannitol were PDX-10-71 and 72; is that correct,**
:27:19 **Dr. Winter?**
:27:19 A. **That's correct, yes.**
:27:20 Q. **And so, Dr. Winter, in your opinion, would a person of**
:27:23 **ordinary skill in the art in 2005 have increased both the**
:27:28 **amount of mannitol as compared to Ribomustin and reduce the**
:27:33 **volume of diluent in order to improve the reconstitution**
:27:38 **time of Ribomustin?**
:27:39 A. **No, not at all, and I've tried to make clear that what**
:27:44 **has been provided here and what is sort of textbook**
:27:49 **knowledge would have pointed in the opposite direction.**
:27:51 Q. **So in your opinion, Dr. Winter, was the subject matter**
:27:56 **of Claim 1 of the '756 patent obvious in 2005?**
:27:59 A. **No, not at all.**
:28:02 Q. **If we could now turn, Dr. Winter, to Claim 4 of the**
:28:07 **'756 patent. Is there a requirement with respect to a vial**
:28:11 **size in Claim 4 of the '756 patent?**

:28:14 A. **Yes. It says we should have that in a 20-millimeter**
:28:19 **vial.**
:28:19 Q. **Now, do you recall Dr. Kwan's testimony that there**
:28:24 **would have been a general motivation to decrease vial size**
:28:26 **in order to improve economic efficiency relating to**
:28:30 **lyophilized pharmaceutical products?**
:28:32 A. **I do well agree that, well recognize that.**
:28:35 Q. **All right. Do you agree with him?**
:28:39 A. **I agree partly with him because in considering**
:28:44 **manufacturing aspects, it is a due reason to go forth**
:28:51 **smaller vials, but there are different other aspects to**
:28:55 **consider, so we have to be careful in that judgment.**
:29:00 Q. **All right. And have you prepared a slide to walk us**
:29:03 **through what the additional considerations might be to a**
:29:06 **person of ordinary skill in the art?**
:29:07 A. **Yes. And it's already up there.**
:29:11 Q. **This is PDX-10-74, Dr. Winter; is that right?**
:29:16 A. **It is.**
:29:16 Q. **So, Dr. Winter, what considerations would have a**
:29:22 **person of ordinary skill in the art taken into account**
:29:25 **before reducing the vial size of Ribomustin?**
:29:29 A. **Would have, of course, taken into account this aspect**
:29:33 **that you now get an increased number of vials into a given**
:29:37 **lyophilizer, which we just heard before, but with that we**
:29:42 **have to consider in parallel that the smaller vials now**

restrict us to other volumes, and if we might then reduce the volume we put into that vial, we may change the cake density. We may change the cycle time into what direction it's open in my opinion.

And the last part I already said. We have to decrease diluent volume, which is also possible afterwards to offer to the, the healthcare professionals, and by that, we discussed that before. At least from principles, we have to consider increased reconstitution time.

Q. So if a person of ordinary skill in the art in 2005 was concerned about the reconstitution time of Ribomustin, would that person have considered using a smaller vial in your opinion?

A. Not at all.

Q. Why not?

A. Because the expectation and the basics of thermodynamics and dissolution of the solid matter in solvents points in the opposite direction.

Q. So, Dr. Winter, in your opinion, was the subject matter of Claim 4 of the '756 patent obvious to a person of ordinary skill in the art in 2005?

A. It was not obvious.

Q. If we could now turn to the last patent that you're discussing in your testimony today, which is the '270

:31:24 **patent. And I want to direct your attention, Dr. Winter, to**
:31:29 **the '270 patent, which I believe is JTX-005, and in**
:31:37 **particular, to Claims 1, 3, 5, 7, 19 through 21.**
:31:41 A. **Yes.**
:31:43 Q. **And on PDX 10-76, which has an excerpt of those**
:31:49 **claims, do you see that, Dr. Winter?**
:31:51 A. **I see it, yes.**
:31:52 Q. **All right. What's the general subject matter of the**
:31:57 **claims of the '270 patent that are at issue in this**
:32:01 **litigation?**
:32:02 A. **I'm not going to read through all of it. The subject**
:32:06 **matter is that here we have restrictions or clear limits**
:32:10 **about degradants of bendamustine, HP1, HP1, HP1, and in I**
:32:21 **think Claim 7, it is a general definition of all degradants,**
:32:28 **and we have numbers in percent or part of percent above**
:32:34 **these limits.**
:32:38 Q. **Do you recall Dr. Kwan's testimony that it would have**
:32:40 **been obvious to find a solvent system in 2005 that would**
:32:43 **produce a lyophilized product with the claimed degradant**
:32:47 **levels?**
:32:48 A. **I recall that.**
:32:48 Q. **Do you agree with him?**
:32:50 A. **No, I do not.**
:32:51 Q. **Can you explain why you disagree with him?**
:32:53 A. **Because, first of all, nothing pointed to this**

specific purity level that is claimed here in the patent claims. And it is impossible, in my opinion, to predict how organic solvents would lead to these specific impurity levels that are claimed there. And even if the solvents or co-solvents would have stabilized the so-called bulk solution or pre-lyo solution, even further it would have been impossible to predict for the POSA how that would now impact on the resulting lyophilized product.

Q. Now, Dr. Welton has already testified about degradation, so I want to focus your testimony on the last point you discussed, which is the impact of the solvent system.

Does the selection of a solvent system impact issues other than just the stability of a pre-lyophilization solution?

A. Absolutely, yes.

Q. And what are some of the other potential impacts of a solvent on the lyophilized product and lyophilization of a pharmaceutical product?

A. I put most important effects up on this slide again, and, of course, there are the certain redundancies to what we have discussed earlier. That is solvent now picked out as one of the major solid composition of formulation element can affect, I'm not going to read all these effects: Fill volume, lyophilized product stability, which is for me the

:34:49 most important, and all the other parameters and factors we
:34:53 see around the circle here.
:34:54 Q. Now, you said that lyophilized product stability was
:34:58 for you the most important one. Can you explain why?
:35:01 A. Yes. Because by concept, if we go for lyophilization,
:35:08 we have considered earlier our conversation that we only do
:35:14 this when the liquid form is not applicable, because the
:35:18 liquid form would be the way to go anyway. And then we have
:35:24 to see whether now with the matter or with the tools using
:35:30 lyophilization, we would have come up with a stable product
:35:35 because we would have not ended up with a liquid stable
:35:39 product, and therefore this is the most important aspect to
:35:43 see and to achieve. Do we achieve a stable product after
:35:48 the process of course ends after the storage time, which is
:35:52 typically two years, maybe longer, for such a product?
:35:01 Q. What would the person of ordinary skill in the art in
:35:37 2005 need to do to see if their lyophilized composition had
:35:42 the product stability that they wanted?
:35:44 A. Would define formulations, try them out in
:35:49 experiments, meaning lyophilize them, and then store them
:35:52 for a significant period of time, then analyze them.
:35:57 Q. Would the person of ordinary skill in the art have had
:36:00 a reasonable expectation of succeeding in that endeavor with
:36:05 the particular solvent before they did those experiments?
:36:08 A. No. They have to do these experiments I just

explained.

Q. So, Dr. Winter, in your opinion, were the asserted claims of the '270 patent obvious to a person of ordinary skill in the art in 2005?

A. No, they were not.

Q. Now, Dr. Winter, do you recall from the testimony of Drs. Kwan and Kamat, their repeated reference that routine optimization or experimentation would have led to a number of the elements of the claimed inventions that we have discussed today?

A. I recall this very well, yes.

Q. Do you agree with them?

A. No, I do not.

Q. Why not?

A. Because this picture they paint that it's just routine optimization and you would more or less automatically have upward results like here, as is claimed in these claims, is not describing the situation well and correct enough.

I think I tried to make clear, especially by referring to Teagarden, how complex the situation is, and also in the last few minutes about choosing the right amount of mannitol, that we do not have reasonable expectation of success. Therefore, we have to do experiments that are far from routine. They require at least a POSA, if not a more experienced person, to end up with the improved results.

:37:57 **MR. MITROKOSTAS: Thank you, Dr. Winter. I have**
:37:59 **no further questions at this point.**
:38:00 **THE COURT: All right. Your witness.**
:38:02 **CROSS-EXAMINATION**
:38:03 **BY MR. CWIK:**
:38:03 Q. **Good morning, Dr. Winter.**
:39:12 A. **Good morning.**
:39:13 Q. **Dr. Winter, I want to talk a little bit first about**
:39:17 **your experience with TBA, tert-butanol alcohol.**
:39:23 **Now, in your 27 years of experience, you have**
:39:26 **personally never used TBA as a co-solvent in a commercial**
:39:29 **product. Is that correct?**
:39:31 A. **That's correct.**
:39:31 Q. **And in your 27 years of experience, you have also**
:39:38 **never used a co-solvent system in connection with a**
:39:42 **lyophilized commercial product. Correct?**
:39:45 A. **With a commercial product, no. Other products, yes.**
:39:49 Q. **And you did a thesis for your Ph.D. Correct, Dr.**
:39:57 **Winter?**
:39:58 A. **Yes, of course.**
:39:59 Q. **And different from Dr. Kamat, your thesis did not**
:40:03 **address lyophilization. Correct?**
:40:05 A. **No.**
:40:05 Q. **And different from Dr. Kamat, your thesis did not**
:40:10 **address lyophilized products. Correct?**

:40:12 A. **No.**
:40:13 Q. **It did address lyophilized products?**
:40:18 A. **No, no. My doctoral thesis did not address lyophilized product.**
:40:22 Q. **And it did not address lyophilization. Correct?**
:40:25 A. **No.**
:40:25 Q. **When I say correct, it means --**
:40:30 A. **I have to say yes.**
:40:34 Q. **Very good.**
:40:35 A. **I am sorry. I think it was clear what I meant.**
:40:37 Q. **Doctor, you would agree that you are not a pharmaceutical chemist. Correct?**
:40:47 A. **I agree to that, although I might take your attention to that in America, what we do, studies in pharmacy are often called pharmaceutical chemistry of drugs. We in Germany and Europe call it pharmacy.**
:41:07 **I just want to remind the Court that there might be differences in the curriculum. But I am not going to expand on that to you.**
:41:17 Q. **Doctor, you do not consider yourself an expert in FDA regulatory compliance. Correct?**
:41:23 A. **Not an expert. But I have had my experience.**
:41:27 Q. **And you personally have never performed batch analysis on any pharmaceutical product for regulatory purposes. Correct?**
:41:35

:41:37 A. **Not personally. But I said before that we have**
:41:41 **brought a product to the market when I was the responsible**
:41:45 **person for the freeze-dried product. And my dear colleagues**
:41:51 **provided me with this data I just referred to, and I was**
:41:55 **responsible to bring these data into a report I personally**
:42:00 **wrote and submitted to the FDA.**
:42:05 Q. **Let's talk about the Ribomustin product. You would**
:42:07 **agree that the Ribomustin product was widely used before**
:42:11 **2005. Correct?**
:42:13 A. **I agree to that, yes.**
:42:14 Q. **And during their analysis of various Ribomustin lots,**
:42:23 **the inventors on these patents found that reconstitution**
:42:26 **time could take anywhere between 30 and 45 minutes.**
:42:29 **Correct?**
:42:31 A. **This is not exactly what I have seen in documents that**
:42:36 **have been provided to me.**
:42:37 Q. **Do you recall testifying during your deposition that**
:42:43 **during their analysis of various Ribomustin lots, the**
:42:46 **inventors found that reconstitution time could take anywhere**
:42:50 **between 30 and 45 minutes?**
:42:53 A. **Yes.**
:42:54 Q. **And you did state that. Correct?**
:42:57 A. **This may well be. I trust you and we don't need to**
:43:02 **look that up. I recall as well that during my deposition I**
:43:06 **think you have confronted me with the original documents**

about that. And that was a little bit different, as far as I recall.

Do you want me to outline on that?

Q. I think you confirmed my question.

You would agree that there is a general desire to reduce very long reconstitution time. Correct?

A. That's correct, yes. I agree to that general statement.

Q. And a formulator designing a lyophilized product generally would want to have a product with a reconstitution time less than 30 to 45 minutes. Correct?

A. I generally agree to that statement, yes.

Q. Doctor, I would now like you to take a look at your exhibit binder that we have handed you. Specifically, if you could look at Exhibit No. DTX-576. I believe they are in numerical order, if that helps.

A. That is the Ribomustin product monograph. Is that correct?

Q. That's correct.

A. I am there.

Q. You recognize this as the Ribomustin product monograph. Correct?

A. Yes.

Q. I would like you to now take a look at the eighth page of that exhibit. On the bottom of that eighth page it has a

:44:38 **page number of DTX-576.0008?**

:44:45 A. **Yes, I am there.**

:44:47 Q. **Do you see there is a Section 2.6? Correct?**

:44:54 A. **I am just confused. It is on the screen, but I prefer to go to the document. I see the Section 2.6.**

:45:00 Q. **And in the bottom paragraph of that section, do you see there is a paragraph that says, "As soon as a clear solution is obtained (this usually takes 5 to 10 minutes) dilute the total dose of Ribomustin immediately with .9 percent sodium chloride solution to produce a final volume of about 50 milliliters"?**

:45:32 **Do you see that sentence?**

:45:34 A. **Yes, but you said 50 milliliters. It is 500.**

:45:39 Q. **And when that paragraph is referring in the parentheses to this usually takes five to ten minutes, it's talking about the reconstitution time to reconstitute the Ribomustin cake. Correct?**

:45:55 A. **That's correct.**

:45:57 Q. **And if a formulator was reading this paragraph, they would then suspect that the reconstitution time could sometimes take longer than five to ten minutes. Is that correct?**

:46:14 A. **I don't know what he would have speculated. But he may have considered that a few times it takes longer, the same probability would be that it takes less time. But I**

don't disagree that he might have speculated about what "usually" means.

Q. Okay. Doctor, could you please turn to DTX-438 in your exhibit binder.

A. Yes, I am there.

Q. And do you recognize this document as the textbook titled Lyophilization - Introduction and Basic Principles, by Thomas A. Jennings?

A. Yes, I identify it as such.

Q. You cited this textbook in your own expert report. Correct?

A. Yes.

Q. I would like you to take a look at the Page No. DTX-438,447. The last three numbers are 447?

A. Yes, I am there.

Q. And you see there is a paragraph, bottom middle, starting with the words "Some products"?

A. I see this paragraph.

Q. And looking at the third sentence, do you see the third sentence says, "However, if the reconstitution time is excessive (e.g., greater than three minutes) then the user may run out of patience or become frustrated and resort to shaking the vial to accelerate the reconstitution process"?

Do you see that?

A. I see it, yes.

Q. **Did you cite that language in your expert report?**
A. **I am not sure whether I cited that language.**
MR. MITROKOSTAS: Objection, Your Honor. I don't know what the relevance is.
THE COURT: I am not sure about the relevance. I am not sure that's a fair question. Do you want to give him some context?
MR. CWIK: I will continue, Your Honor.
BY MR. CWIK:
Q. **Doctor, do you see the last paragraph -- the last sentence of this paragraph as well?**
A. **I see it, yes.**
Q. **That sentence says, "If a product requires more than five minutes to reconstitute, then steps should be taken to decrease the reconstitution time rather than depending on the patience of the user."**
Do you see that?
A. **I see it.**
Q. **Is this textbook inconsistent with your opinions?**
A. **What my opinions are with respect to Ribomustin, I must explain in the context of these two sentences, in two or three sentences, if you will allow, because the context of Ribomustin is to be used -- the product is to be used in a setting that must, as explained to us very clearly, that this is a product for severely ill patients. When the**

:49:40 hospital pharmacies take this lyophilized product, dissolve
:49:45 it according to the instructions in the monograph, then
:49:49 dilute it with sodium chloride, then take -- this is
:49:56 state-of-the-art procedure for oncological products --
:50:01 adjust the dose to the body weight or even better the body
:50:06 surface of the patient, all antiseptically, and they bring
:50:11 it to the station wherein the patient is infused.
:50:15 There, it is not about a patient who becomes
:50:20 impatient, because he needs a few minutes to dissolve that,
:50:25 because he is severely ill.
:50:28 So I respect the teaching of Dr. Jennings. But
:50:34 in the context of this particular drug product, we discussed
:50:38 this here, they are not to be applied one to one, as we say
:50:43 in Germany.
:50:46 Q. Doctor, in your direct examination, you noted the
:50:51 differences between the claimed inventions and the
:50:57 Ribomustin formulation. Correct?
:50:58 A. Yes.
:50:58 Q. I would like you to take a look at DTX-356 in your
:51:06 exhibit binder.
:51:15 A. Yes, I am there.
:51:17 Q. And the title at the top of this document is
:51:20 Investigational New Drug Application. Correct?
:51:24 A. That's correct.
:51:24 Q. And the name of the sponsor is Salmedix, Inc.

Correct?
A. Correct.
Q. And in Box 6 it says the name of the drug is SDX-105 for injection (bendamustine hydrochloride). Correct?
A. That's correct.
Q. And you did not consider this document in forming your opinions. Correct?
A. Yes, because it is not prior art.
Q. Okay. I would like you to turn to Page 28 of this document?
THE COURT: Which tab are we at, Mr. Cwik?
MR. CWIK: We are still at Exhibit DTX-356, Page 28.
THE WITNESS: Which numbering system?
BY MR. CWIK:
Q. On the bottom it would be Page DTX-356.00028.
A. Okay, now I am there.
Q. And do you see there is a Section 7.0.5.2, Drug Product?
A. Yes, I see this section.
Q. And do you see the last sentence of this section says, "This minor formulation change also improves appearance of the cake and reconstitution efficiency over that of the Fujisawa drug product"?
A. I see and read this text, yes.

:53:05 Q. **And we have a slide on this as well, if we could bring**
:53:12 **that up.**
:53:13 **This, Dr. Winter, is a callout or a blowup of**
:53:21 **the last few sentences of that same paragraph we were**
:53:24 **reading. Do you see that this paragraph also discusses the**
:53:31 **changes from the Fujisawa drug product to the product at**
:53:37 **issue in this Investigational New Drug Application?**
:53:44 A. **Just to make sure, where is this blown up? From the**
:53:47 **same page?**
:53:48 Q. **Yes.**
:53:49 A. **Okay. Thank you. Yes. I agree with what it is.**
:53:54 Q. **And do you agree that this same paragraph that**
:53:58 **discusses a minor formulation change describes one change as**
:54:03 **TBA instead of ethanol. Correct?**
:54:07 **MR. MITROKOSTAS: Your Honor, I am going to**
:54:09 **object to this line of cross-examination. The witness**
:54:11 **testified that this isn't prior art. It doesn't really bear**
:54:15 **on his opinions as to --**
:54:17 **THE COURT: Sustained.**
:54:17 **BY MR. CWIK:**
:54:51 Q. **Doctor, let's talk about bulking agents. You would**
:54:58 **agree that adding bulking agents adds additional mass**
:55:05 **and physical structure to a lyophilized cake; is that**
:55:07 **correct?**
:55:07 A. **I agree with that statement.**

:55:11 Q. **And bulking agents can impact cake quality; is that right?**

:55:16 A. **I agree.**

:55:17 Q. **And that fact was known to a person of ordinary skill in the art prior to 2005; is that correct?**

:55:23 A. **Correct as well.**

:55:25 Q. **And cake quality impacts the amount of reconstitution time; is that correct?**

:55:31 A. **The amount of reconstitution time with our formulation, the reconstitution time.**

:55:44 Q. **It affects the length of --**

:55:45 A. **Yes, yes. I'm sorry.**

:55:47 Q. **And that fact was also known to a person of ordinary skill in the art prior to 2005; is that correct?**

:55:51 A. **That cake quality can affect reconstitution time, I agree.**

:56:01 Q. **And you would agree that the most used bulking agent for lyophilization prior to 2005 was mannitol; is that correct?**

:56:07 A. **Agreed.**

:56:08 Q. **And you understand that sucrose was also a bulking agent prior to 2005; is that correct?**

:56:15 A. **Yes.**

:56:16 Q. **Now, let's talk about the final cake in a lyophilized product.**

:56:26 **You would agree that a final cake in a**
:56:29 **lyophilized product is filled with microscopic pores most of**
:56:34 **the time; is that correct?**
:56:36 A. **I agree.**
:56:38 Q. **And those pores serve to greatly increase the surface**
:56:43 **area of the cake and therefore assist in the reconstitution**
:56:47 **process; is that correct?**
:56:47 A. **First part of the statement, correct. Second, not**
:56:53 **necessarily.**
:56:54 **I personally work scientifically on that**
:56:59 **subject, and not in every case do more pores lead to a**
:57:09 **faster reconstitution. This is a very complicated matter**
:57:10 **where -- well, wetting, capillary forces, and, of course,**
:57:17 **the dissolution kinetics of the material as such, are as**
:57:25 **rightfully said, the pores and the numbers. What is not**
:57:30 **unidirectional consequence in a way more pores, this and**
:57:36 **that, or smaller pores. This is not in every case.**
:57:39 Q. **I understand it may not be in every case, but would**
:57:43 **you agree that in most cases, the addition of more pores**
:57:48 **increases the surface area and therefore assists in the**
:57:51 **reconstitution process?**
:57:52 A. **This is in the majority of the cases, correct.**
:57:59 Q. **And that fact was also known to a person of skill in**
:58:03 **the art prior to 2005; is that correct?**
:58:05 A. **Yes.**

:58:06 Q. **And the amount and size of the pores that exist in the**
:58:14 **cake are known as porosity; is that correct?**
:58:16 A. **The amount of pores. Porosity is a general term and**
:58:25 **it's, first of all, not related to the amount. The volume**
:58:31 **of pores versus the volume of the solid matter. It does not**
:58:33 **in the first place about further, let's say definition,**
:58:36 **relate to the size of the pores. Particular detail, I'm not**
:58:43 **sure what you would like me to work out on that.**
:58:45 Q. **That is okay. And higher porosity values are**
:58:50 **typically associated with higher cake surface areas; is that**
:58:54 **correct?**
:58:54 A. **Yes, I agree.**
:58:57 Q. **And higher porosity values are typically associated**
:59:01 **with faster reconstitution times; is that correct?**
:59:05 A. **We had that before, and I cautioned, the majority of**
:59:11 **the cases, this is the right direction, and I cautioned the**
:59:17 **laboratory that we do have often other effects that overrule**
:59:21 **that, and therefore I would not bet on this rule to apply to**
:59:29 **each cake.**
:59:31 Q. **And you would agree that it is important for a product**
:59:35 **formulator to consider whether the lyophilized cake**
:59:39 **reconstitutes readily under clinical conditions; is that**
:59:42 **correct?**
:59:42 A. **This is a general consideration that is important,**
:59:47 **yes.**

:59:47 Q. **And that fact was also known to a person of ordinary**
:59:50 **skill in the art prior to 2005; is that correct?**
:59:52 A. **This concept was known, yes.**
:59:55 Q. **Let's talk about the solubility of the cake and the**
:00:02 **reconstitution medium.**
:00:06 **Do you agree that the solubility of the**
:00:10 **lyophilized cake in the dissolution medium will determine**
:00:14 **the saturation point for a given volume in a reconstitution**
:00:18 **media; is that correct?**
:00:19 A. **I'm not sure whether this sentence was correctly**
:00:26 **formulated because I'm was not sure what that term was, what**
:00:32 **direction. At least maybe rephrase it or repeat it step by**
:00:37 **step --**
:00:37 Q. **Okay.**
:00:38 A. **-- so I'm sure that I answer it scientifically**
:00:41 **correct.**
:00:41 Q. **Sure. You agree that the solubility of the**
:00:44 **lyophilized cake in the dissolution medium will determine**
:00:50 **the saturation point for a given volume of reconstitution**
:00:54 **media?**
:00:54 A. **No. This is what I assumed. It's the other way**
:00:57 **around. The saturation point and the solubility, this is**
:01:07 **sort of the same thing but expressed in different words, so**
:01:09 **they do not determine each other. They do have an**
:01:14 **equilibrium solubility. This is physical chemical term**

known for a hundred or more years. As a matter of fact, I can work on that, but I don't think that you want me to.

Q. Well, Doctor, let me ask it this way: Do you recall in your expert report stating, quote, "The solubility of the lyophilized cake in a dissolution medium is an important factor because it will determine saturation point for a given volume of reconstitution media," period, end quote?

THE COURT: Just a second, Doctor.

Yes, Mr. Mitrokostas?

MR. MITROKOSTAS: I don't know what page Mr. --

THE COURT: Okay.

MR. CWIK: Sure. That was Paragraph 138, Page 156.

MR. MITROKOSTAS: Paragraph 138?

Your Honor, I'm going to object as to whether this is appropriate impeachment, but with his expert report. I don't know if he has established what Dr. Winter has done here is inconsistent with what he said. At the very least, Dr. Winter should be able to see his report.

THE COURT: That's fair, and then you can proceed with the question.

MR. CWIK: All right.

(Report handed to the witness.)

THE WITNESS: Thanks a lot. Can you help me

:03:02 **with the --**

:03:03 **BY MR. CWIK:**

:03:03 Q. **Yes, Doctor. It's Page 56?**

:03:06 **THE COURT: Your colleague is showing him.**

:03:07 **(Pause.)**

:03:10 **THE WITNESS: Yes, I see it. I accept, I might have expressed that as well not in the best way, but we can work that out what it means.**

:03:23 **BY MR. CWIK:**

:03:24 Q. **Okay, Doctor. And would you also agree that once the concentration of a lyophilized cake reaches a material level, for example, 10 to 15 percent of the reconstitution solution saturation point, the dissolution rate will continuously slow as the concentration of the dissolved material increases?**

:03:47 A. **Was there a question?**

:03:53 Q. **Yes.**

:03:53 A. **You were reading.**

:03:54 Q. **Do you agree with that statement?**

:03:56 A. **Yes.**

:04:00 Q. **And the implication from that statement is that the dissolution rate of a lyophilized cake can be improved by increasing the dissolution volume to push the reconstitution solution closer to sink conditions; is that correct?**

:04:17 A. **Correct.**

:04:19 Q. **Doctor, let's change topics a little bit here.**

:04:26 **Now, let's talk about the stability of the**

:04:28 **products used in lyophilization process.**

:04:33 **You would agree that lyophilization can prevent**

:04:37 **unstable drugs from degrading during storage; is that**

:04:41 **correct?**

:04:41 A. **I agree.**

:04:42 Q. **And that fact was known to a person of ordinary skill**

:04:50 **in the art prior to 2005?**

:04:52 A. **Yes.**

:04:52 Q. **And you would agree that using lyophilization to**

:04:57 **prevent unstable drugs from degrading during storage is**

:05:01 **especially important when highly reactive drugs such as**

:05:05 **anti-cancer alkylating agents like bendamustine are used; is**

:05:09 **that correct?**

:05:09 A. **This is one example where this is relevant, yes. Of**

:05:18 **course, other groups as well.**

:05:21 Q. **And you would agree that a formulator has to consider**

:05:25 **product impurities in developing a drug for human use; is**

:05:29 **that correct?**

:05:29 A. **Yes.**

:05:30 Q. **And you would agree that prior to 2005, bendamustine**

:05:35 **was reported to degrade when placed in water; is that**

:05:39 **correct?**

:05:39 A. **I agree.**

:05:40 Q. **And you would agree that in formulating pharmaceutical**
:05:45 **products, a formulator has a general will to eliminate the**
:05:51 **degradants in a product as much as possible; is that**
:05:54 **correct?**
:05:54 A. **That's possible, yes.**
:05:56 Q. **And you would agree that prior to 2005, there would**
:06:02 **have been a high probability that a person of ordinary skill**
:06:05 **in the art would have considered the effect of hydrolysis in**
:06:09 **a pre-lyo solution in developing a formulation of**
:06:14 **bendamustine; is that correct?**
:06:15 A. **I agree.**
:06:22 Q. **And you spoke about the Maas and Gust references**
:06:28 **earlier today; is that correct?**
:06:29 A. **Yes, I did.**
:06:30 Q. **And you agree that both Maas and Gust address**
:06:34 **bendamustine degradation; is that correct?**
:06:36 A. **What? I didn't hear the word.**
:06:39 Q. **You would agree is that the Maas and Gust references**
:06:43 **both address --**
:06:44 A. **Address, yes.**
:06:45 Q. **-- bendamustine degradation; is that correct?**
:06:48 A. **No. For Maas, I agree. For Gust, he does not**
:06:56 **directly address bendamustine degradation. He serves, let's**
:07:03 **say as a background, synthetic chemist and analytic chemist**
:07:08 **to provide us with his degradation products and the**

:07:13 **reference samples and so on, but he not further studies the**
:07:17 **degradation of the substance.**
:07:19 Q. **And Maas addresses bendamustine degradation in aqueous**
:07:35 **solution; is that correct?**
:07:36 A. **Yes.**
:07:38 Q. **And Gust characterizes degradation analytically; is**
:07:45 **that correct?**
:07:45 A. **Degradation products, yes.**
:07:49 Q. **Now, let's talk about the reconstitution properties**
:07:57 **existing in a lyophilized product.**
:08:04 **Concerning lyophilization, you would agree that**
:08:07 **a person of ordinary skill in the art would have known that**
:08:10 **lyophilization can enhance reconstitution properties; is**
:08:14 **that correct?**
:08:14 A. **I agree, but we should then put the relative basis**
:08:23 **into light relative to what increase may be to a**
:08:28 **non-lyophilized product which is being received by whatever**
:08:33 **different drying technology or so. And I fully agree.**
:08:38 Q. **Because there are other drying techniques other than**
:08:42 **lyophilization; is that correct?**
:08:43 A. **Yes.**
:08:43 Q. **And among the reconstitution properties that can be**
:08:47 **enhanced are the time and completeness of the**
:08:51 **reconstitution; is that correct?**
:08:53 A. **Yes.**

Q. **And you would agree that the lyophilization process can enhance a product in such a way that the reconstitution process is faster than it would be using other drying processes; is that correct?**

A. **It can, yes.**

Q. **Okay. I'd like to now look at the Teagarden reference, which is Exhibit 999 in your exhibit binder.**

A. **Yes, I have it in front of me.**

Q. **And this is the same Teagarden reference you discussed earlier this morning; is that correct?**

A. **Yes.**

Q. **Now, Doctor, you duly accept Teagarden as a reasonable piece of work; is that correct?**

A. **I do.**

Q. **And the Teagarden article appears in the European Journal of Pharmaceutical Sciences; is that correct?**

A. **Correct.**

Q. **And that journal is a well-respected journal. Correct?**

A. **It is.**

Q. **And the articles in this journal are peer-reviewed. Correct?**

A. **Correct.**

Q. **Now, on the first page of Teagarden, do you see there is an abstract, Doctor?**

:09:49 A. **Yes, I see it.**

:09:53 Q. **And about halfway down there is a sentence that**

:09:59 **begins, "The co-solvent."**

:10:05 **Do you see that sentence?**

:10:06 A. **Yes.**

:10:06 Q. **That sentence says, "The co-solvent system that has**

:10:10 **been most extensively evaluated was the tert-butanol/water**

:10:16 **combination."**

:10:19 **Do you see that sentence?**

:10:20 A. **I see that.**

:10:20 Q. **And you generally agree with that statement from**

:10:23 **Teagarden. Correct?**

:10:25 A. **That it has been the most extensively evaluated**

:10:31 **co-solvent system. I agree with that.**

:10:36 Q. **And the next sentence continues, "The tert-butanol**

:10:41 **possesses a high vapor pressure."**

:10:46 **Correct?**

:10:46 A. **I can read that, correct.**

:10:49 Q. **And you agree that high vapor pressure is a desirable**

:10:53 **attribute of tert-butanol. Correct?**

:11:00 A. **With respect to the solvent to be dried out.**

:11:06 **Otherwise, high vapor pressure is not per se a positive**

:11:10 **feature of anything.**

:11:14 **You have to have it in a context. I remind you,**

:11:25 **on Teagarden, I have forgotten the page, but I can find it,**

:11:29 **where he tells us an interesting story about the very high**
:11:33 **vapor pressure of these solvents that leads to complications**
:11:37 **during the pre-freezing phase in the lyophilizer, when**
:11:45 **material evaporates and flows down the vial and creates haze**
:11:48 **on the vial side and so on. Just to make that relative,**
:11:56 **that per se vapor pressure is not an undisputed,**
:12:01 **unidirectional feature.**
:12:03 Q. **Doctor, so I understand your testimony, you would**
:12:09 **agree with me that high vapor pressure can be at least a**
:12:13 **desirable attribute of tert-butanol. Would you agree?**
:12:16 A. **I would agree.**
:12:17 Q. **And prior to 2005, you understood tert-butanol to**
:12:23 **freeze completely in most commercial freeze dryers.**
:12:26 **Correct?**
:12:26 A. **Yes.**
:12:27 Q. **And that's a positive attribute of TBA. Correct?**
:12:33 A. **In the context you just discussed, if you want to**
:12:36 **freeze-dry it, it is a positive attribute.**
:12:44 Q. **And, continuing on this sentence within the abstract,**
:12:53 **the sentence that has the high vapor pressure also continues**
:12:58 **and says that, "Tert-butanol can increase sublimation**
:13:03 **rates."**
:13:04 **Correct?**
:13:05 A. **Yes, correct.**
:13:06 Q. **And that was known to a person of ordinary skill in**

:13:09 **the art prior to 2005. Correct?**

:13:12 A. **Yes.**

:13:12 Q. **And the Teagarden abstract also says that tert-butanol**

:13:19 **has a low toxicity.**

:13:22 **Correct?**

:13:23 A. **Yes, it says there.**

:13:24 Q. **And a person of ordinary skill in the art would have**

:13:29 **generally known that tert-butanol had a reputation for low**

:13:33 **toxicity prior to 2005. Correct?**

:13:40 A. **Let's put it this way: It's not about a reputation.**

:13:44 **It's when you take this review and read it carefully, you**

:13:48 **would agree with that statement. And so far, we agree with**

:13:52 **each other. But I have a problem with the word reputation**

:13:59 **in the context of this TBA.**

:14:02 Q. **All right. If we could take a look at Table 2 in**

:14:06 **Teagarden, Dr. Winter. It's on Page DTX-0999.0003.**

:14:18 A. **Yes, I am there. I have it in front of me.**

:14:21 Q. **And Table 2 from Teagarden discusses the use of**

:14:31 **co-solvent systems in a variety of drug preparations.**

:14:36 **Correct?**

:14:37 A. **That's correct.**

:14:37 Q. **And you would agree that eight of those drug products**

:14:47 **are discussed in the context of being used with a**

:14:50 **tert-butanol-water co-solvent system. Correct?**

:14:53 A. **I agree. But I have to make one remark. It's a**

:14:59 **detail, but it's not an unimportant one, that you spoke**
:15:03 **about drug products. And I have looked up a little bit what**
:15:07 **this is, and I have found at least that a few of those**
:15:12 **examples, in fact, do not refer to drug products, which is**
:15:18 **in our understanding a formulation, like the lyophilized**
:15:26 **product bendamustine or what can be given to the patient,**
:15:30 **but it's in fact API, you know, it's the dried pure drug**
:15:35 **substance, which has a long way to go to become a drug**
:15:39 **product in the end.**
:15:41 **So just to apply some caution that he has put**
:15:47 **together here dutifully, but when you go to the articles,**
:15:53 **you find that in certain cases it's not really about a drug**
:15:58 **product. It's pure drug substance. Then we step into an**
:16:03 **area which is a bit away from where we are here into the**
:16:06 **area of manufacturing of pure drug substances, APIs, just to**
:16:13 **remind you to be correct in that.**
:16:16 **I am sorry, Your Honor, that I took some time**
:16:18 **off.**
:16:19 Q. **Doctor, could you refer to Exhibit DTX-338 in your**
:16:25 **exhibit binder, please.**
:16:38 A. **Yes, I have it here.**
:16:40 Q. **And do you see that DTX-338 is a portion of a book**
:16:48 **entitled Freeze-Drying/Lyophilization of Pharmaceutical and**
:16:55 **Biological Products"?**
:16:57 A. **Yes, I see it.**

Q. **And before your deposition in this case, you had seen this book in your office or library. Isn't that correct?**

A. **That's correct.**

Q. **And the first listed editor of this book is Louis Rey. Correct?**

A. **Yes, it is.**

Q. **And Louis Rey has the reputation as one of the grand old masters in freeze-drying. Isn't that correct?**

A. **Thank you for citing my deposition words.**

I agree.

Q. **And on Page 3 of this book from Mr. Rey, he includes an entire chapter from Teagarden. Correct?**

A. **This is correct.**

Q. **And the title of that chapter is Practical Aspects of Freeze-Drying of Pharmaceutical and Biological Products using Nonaqueous Co-Solvent Systems. Correct?**

A. **This is correct. If I may inform the Court that it is more or less a copy of another article.**

Q. **More or less a copy of the Teagarden article itself?**

A. **Yes.**

Q. **Is that what you said?**

A. **Yes. This is what I said. But it might not be 100 percent. But it is more or less a copy.**

Q. **So Dr. Rey thought the Teagarden article was important enough to include it in his textbook. Correct?**

:18:44 **MR. MITROKOSTAS: Objection, Your Honor. He is asking about the state of mind of Dr. Rey.**

:18:50 **MR. CWIK: I will withdraw it.**

:18:57 **BY MR. CWIK:**

:18:57 Q. **Doctor, can you please take a look at the Ni reference in your book. It is Exhibit JTX-79.**

:19:12 A. **I have it in front of me.**

:19:13 Q. **You discussed the Ni reference earlier this morning. Correct?**

:19:17 A. **I did, yes.**

:19:19 Q. **And you have agreed that Ni generally recommends using TBA for freeze-drying with water-unstable drugs. Correct?**

:19:33 A. **I don't recall that I said Ni generally recommends that.**

:19:42 **I am not sure, so I better not agree until I have looked that up.**

:19:58 Q. **Doctor, do you recall in your deposition testifying that Ni recommends using TBA for freeze-drying with water-unstable drugs?**

:20:10 A. **Yes, that would be correct.**

:20:14 Q. **So you do or do not recall stating it?**

:20:18 A. **I do not recall exactly that sentence. I have to look it up in my deposition. It could well be, because it sounds not implausible. If you want, I have to look that up.**

:20:32 Q. **Would it help if we gave you a copy of your**

deposition?

THE COURT: I think he has it.

THE WITNESS: I have one.

BY MR. CWIK:

Q. Great. Could you please look at Page 107 of your deposition.

A. 107, yes.

Q. Page 107, if you look at the last line, Line 25, do you see where -- actually, starting on Line 23 at Page 107, the question is:

"Okay, so you pointed out something about -- I am not so sure you answered my question. So do you agree that Ni recommends using TBA for freeze-drying with water-unstable drugs?

"Answer: With water-unstable drugs?

"I have to look up whether this term or this goes far."

(Perusing document), which means you were looking at the document. Then you continue:

Yes, she does give a recommendation with a typical due caution that she says "TBA can improve the solubility and stability of hydrophobic and water-sensitive drugs."

Do you see that?

A. I see that, yes. This is exactly what caused me to

look it up again, because it looks like during the deposition, which is two months ago, I had the same feeling, that this generalization has to be taken with caution. I feel very well supported by my previous statement and the caution I took this time.

Q. And Ni describes some experiments that were run in her paper. Correct?

A. Correct.

Q. And the experiments run by Ni and described in her paper are not anything more than normal tests. Correct?

A. What does "anything more than normal" mean? They are scientifically valuable experiments, and I thought I had testified more or less again similarly in the deposition, that that led to a set of data that were words to be published in this paper.

So I don't understand what the term "not more than normal" means. If you apply this term, not more than normal, to daily life, it ends up with a philosophical conundrum of ideas.

So it is a, let's say, a valuable piece of work which, maybe a Ph.D. student she was under the supervision of Dr. Yalkowsky in those years.

Q. Dr. Winter, at your deposition, do you recall testifying that these experiments are not more than normal?

MR. MITROKOSTAS: I am going to object again. I

don't know that Mr. Cwik has established that he has impeached himself at all from his deposition. He just explained his testimony in the context of the deposition.

THE COURT: I am going to let the Doctor answer the question. You should let the Doctor answer the question.

THE WITNESS: Okay. So the question was?

BY MR. CWIK:

Q. Doctor, I can repeat that.

Do you recall testifying in your deposition that the experiments from Ni are not more than normal?

A. I don't recall these words. I have to look it up.

Q. Would it help to look at your deposition then?

A. Yes, of course.

Q. Please take a look at Page 114 then. And specifically, starting on Line 8.

A. Yes, I am there.

Q. You can read that all the way to Page 115, Line 9.

A. Yes. I read it. Again, if you will read this carefully, let's say with a positive mind, you will see that we had argued about terms like excessive, normal, more than normal. I said in the bold part, Before the group composed of university people would do, and so on.

So we are in the same situation now.

Q. All right, Doctor. Let's just read the text itself

for the record.

On Page 114, Line 8, the question begins:

"The experiments that Ni reports in her paper, do you consider these experiments to be excessive experimentation or fairly routine" --

THE COURT: Hold on. Your colleague stood up here.

MR. MITROKOSTAS: Your Honor, this is not appropriate impeachment. The witness has been shown his transcript. He has explained it.

THE COURT: He doesn't agree with you, Mr. Cwik. What is it that you seek to establish now? Tell me. If it is reasonable, I will let you do it.

MR. CWIK: He is interpreting the words of his transcript. I believe they are inaccurate. So we are going to read it together and understand what his reading of it is.

THE COURT: Okay. You can redirect. Okay.

BY MR. CWIK:

Q. I will start again. On Page 114, Line 8:

"Question: The experiments that Ni reports in her paper, do you consider these experiments to be excessive experimentation or fairly routine?

"Answer: What do you mean with 'excessive'? Can you explain that term?

:26:57 **"Question: Well, to a person of ordinary skill**
:26:59 **in the art, would they consider this experimentation to be**
:27:02 **excessive?**
:27:04 **"Objection.**
:27:05 **"Answer: No. I was just asking you as a non-**
:27:08 **native speaker because the term excessive, this is a word I**
:27:12 **typically do not use. Therefore, I was a bit unsure.**
:27:16 **"Okay. Excessive means more than normal.**
:27:19 **"Okay. Yeah, then, I got you right. No, these**
:27:22 **experiments are not more than normal. They are in, let's**
:27:26 **say, the ballpark of what a group composed of university and**
:27:31 **company people would do."**
:27:33 **And it continues.**
:27:34 **Do you see that language?**
:27:35 A. **I see it.**
:27:36 Q. **And you would agree, Doctor, that if you were aware of**
:27:44 **the Ribomustin product prior to 2005 and you wanted to**
:27:49 **reduce some of the impurities, you would have personally**
:27:53 **considered using TBA? Correct?**
:27:56 A. **No, I disagree.**
:28:12 Q. **Doctor, do you recall testifying in your deposition**
:28:42 **that --**
:28:43 **THE COURT: Do you want to give him the page and**
:28:45 **line reference?**
:28:45 **MR. MITROKOSTAS: What page are you on?**

:28:47 **MR. CWIK: Sure, sure. Page 115.**

:28:52 **THE COURT: Lines?**

:28:53 **MR. CWIK: We'll start with line 10.**

:28:57 **THE COURT: Through?**

:28:58 **MR. CWIK: Okay. It says line ten:**

:29:00 **"Question:"**

:29:01 **THE COURT: Line 10 through what?**

:29:02 **MR. CWIK: All the way through Page 116, line**

:29:07 **13.**

:29:07 **THE COURT: Read it to yourself, Doctor.**

:29:09 **THE WITNESS: Just start at 115, line 10?**

:29:12 **MR. CWIK: Yes.**

:29:13 **THE WITNESS: Okay. So I read and then you ask**

:29:15 **me the question?**

:29:16 **THE COURT: Yes. Read it to yourself.**

:29:18 **THE WITNESS: Okay.**

:29:18 **THE COURT: And then we'll let Mr. Cwik ask**

:29:21 **questions.**

:29:21 **(Pause while witness reviewed deposition**

:29:24 **transcript.)**

:29:49 **THE WITNESS: I'm on Page 116 now, so maybe I'm**

:29:56 **ready to take your question.**

:29:58 **BY MR. CWIK:**

:29:58 Q. **Can you please read all the way, Page 116 through line**

:30:04 **13 as well?**

A. **Page 116, line 13. I have read to that point.**
Q. **All right. And does that refresh your recollection that if you were aware of the Ribomustin product prior to 2005 and you wanted to reduce some of the impurities, you would have personally considered using TBA among other choices?**
A. **Among other choices. I think this part is missing in the previous question and I would have -- I would like to point your attention that you started with on Page 115, line 10: Now assume for a hypothetical that you existed, and so on, which was funny enough, because I was existing in 2005. And all of that was under the hypothetical assumption anyway. And then I agree to say that within other considerations, I would have considered TBA.**

And you asked me as well to read Page 116, and I outlined that I had some other ideas to try and some of them being not based on organic solvents at all. This is the conclusive deposition on what I said in that context. So if you ask me to review that, then I should have the right to, to paint a full picture as well.
Q. **And, Doctor, one of the reasons you might have used TBA with bendamustine is because you might have read the Ni reference; is that correct?**
A. **Maybe. It is more likely that I might have read the hypothetical, the Teagarden reference. It's the one**

that was published more obvious from the -- not obvious in the legal sense, but more well distributed than the Ni article.

Q. Okay. If we could look at Page 117 of your deposition, line 10, can you read that? Line 10 through line 20?

A. Yes.

THE COURT: What was the question? Ms. Gunning, would you read back the question, please? Thank you.

(The Court Reporter read back the read question as follows:

"Question: And, Doctor, one of the reasons you might have used TBA with bendamustine is because you might have read the Ni reference; is that correct?")

THE COURT: Can you answer the question, Doctor?

THE WITNESS: Yes. My answer is that I have answered in the deposition in the context of being asked about Ni for ten minutes before, that I might have considered TBA in reference to Ni, and said, well, might be, but maybe even more likely that I have considered it in the context of having read Teagarden. This is all I said.

THE COURT: Okay.

:33:50 **BY MR. CWIK:**

:33:50 Q. **All right. And, Doctor, you discussed Ni in the**

:33:52 **context of Ni using a pure TBA with the drug compound; is**

:34:00 **that correct?**

:34:00 A. **Yes. This is one context of one correlation I made,**

:34:06 **yes.**

:34:06 Q. **And you would agree that TBA is a more expensive**

:34:10 **solvent than to use than water; is that correct?**

:34:13 A. **I agree.**

:34:14 Q. **And TBA was more expensive than water prior to 2005;**

:34:17 **is that correct?**

:34:17 A. **It was.**

:34:18 Q. **So using a co-solvent system with some water would be**

:34:23 **a manufacturing cost savings over 100 percent TBA solvent**

:34:26 **system; is that correct?**

:34:28 A. **Only if you take only the price for the TBA into**

:34:34 **account. We have other factors that go into that which have**

:34:41 **to put all together and then add it up. But I agree that**

:34:46 **looking at that, I agree to your, to your proposal that you**

:34:54 **save manufacturing costs. In the first place, a lot of TBA**

:35:00 **is expensive.**

:35:01 Q. **I'd like to now look at the Olthoff reference that you**

:35:08 **referred to earlier this morning. It's in your exhibit**

:35:12 **binder as JTX-55.**

:35:24 A. **Yes, I'm there.**

:35:25 Q. **And you've reviewed this reference before, Doctor?**
:35:29 A. **I did.**
:35:29 Q. **And you would agree that Olthoff discloses that bendamustine hydrochloride is stable in solutions of monovalent and polyvalent alcohols; is that correct?**
:35:41 A. **Correct.**
:35:42 Q. **And TBA is a monovalent alcohol; is that correct?**
:35:45 A. **This is correct as well.**
:35:49 Q. **And did you -- you testified earlier that the Olthoff product is a liquid ready to inject product instead of a lyophilized product; is that correct?**
:36:06 A. **Yes.**
:36:10 Q. **All right. And are you aware that Dr. Welton previously testified on behalf of Cephalon in this case earlier?**
:36:19 A. **I'm aware of that.**
:36:20 Q. **And did you read that testimony of Dr. Welton?**
:36:22 A. **I read that.**
:36:24 Q. **And do you recall that Dr. Welton previously testified in this trial that Olthoff's teaching the effect of alcohol solvents on bendamustine stability applied to both lyophilized and liquid ready-to-inject formulations?**
:36:41 A. **I don't recall the details, but I think what he meant, what you mean is that solutions of bendamustine in these alcohols have to be considered. Whether they are taken**

alone or whether they are considered in the course of the lyophilizations is what you mean?

Q. Okay.

THE COURT: Mr. Cwik, can we break or do you think you'll be finished relatively soon? I don't want to rush you.

MR. CWIK: I probably have 20 to 30 minutes, your Honor.

THE COURT: Let's take a lunch break.

(Luncheon recess taken.)

- - -

Afternoon Session, 1:37 p.m.

THE COURT: Please take your seats. I apologize for the delay. All right.

BY MR. CWIK:

Q. Good afternoon, Dr. Winter.

A. Good afternoon.

Q. Doctor, you would agree that once a formulator has decided to develop a lyophilized drug product, he must design an experimental regime in order to arrive at a lyophilized formulation that satisfies all the requirements; is that right?

A. I agree.

Q. Would you agree that the standard size lyophilization vials can generally only be filled to 30 to 50 percent the

:48:25 capacity?
:48:26 A. Generally, I agree that they cannot be filled to,
:48:36 let's say, the rim, but I would not agree on the number or
:48:43 percentage of the fill volume as such.
:48:46 Q. You would not agree that 30 to 50 percent?
:48:48 A. No, I would not like to agree to a certain number and
:48:54 percentage.
:48:55 Q. Okay. Could you look at your expert report and page
:49:02 lessen, please.
:49:03 A. Page 11.
:49:05 Q. Page 11, paragraph 24. Do you see the second sentence
:49:20 of paragraph 24 says, Standard size lyophilization vials can
:49:25 generally only be filled to 30 to 50 percent of their
:49:29 capacity?
:49:30 A. Yes.
:49:30 Q. Does that refresh your recollection that that is an
:49:32 accurate statement?
:49:37 A. It refreshes my recollection that I said that, yes,
:49:42 but that in due course would not like to be as exact in
:49:46 these numbers.
:49:47 Q. And that fact means that the minimum vial size that
:49:53 can be used to lyophilize the given formulation will depend
:49:55 on the fill volume; is that correct?
:49:57 A. Yes.
:49:59 Q. And the fill volume is dependent on the maximum

:50:05 **solubility of the API; is that correct?**
:50:09 A. **Fill volume? Yes. Yes.**
:50:17 Q. **And the fill volume is dependent on any excipients in**
:50:21 **the bulk solution at the chosen formulation temperature; is**
:50:25 **that correct?**
:50:25 A. **Only insofar as we have to consider the solubility**
:50:34 **of the excipients as well, and we are limited by the**
:50:38 **solubility of the excipient, then I agree. But this is a**
:50:44 **quite unusual case, that the solubility of the excipient**
:50:49 **dominates the volume of a pre-lyophilized solution, and by**
:50:55 **that, the size of the vial.**
:50:58 Q. **And you would agree that a smaller vial size**
:51:06 **could increase the capacity for the lyophilizer; is that**
:51:10 **correct?**
:51:10 A. **Yes, correct.**
:51:11 Q. **Now, Doctor, in the process of the experimental regime**
:51:19 **for developing a lyophilized product, you would typically**
:51:23 **prepare a whole group of vials to be tested; is that**
:51:27 **correct?**
:51:27 A. **Yes.**
:51:28 Q. **And in this testing of the whole group of vials, it**
:51:36 **would reasonably take a few months to complete that testing;**
:51:40 **is that correct?**
:51:40 A. **At least a few months, yes.**
:51:46 Q. **And in those few months, one would first consider what**

:51:52 you want to do. Then you have to get the materials to make
:51:56 it, essentially lyophilize it, store it, and then dissolve
:52:02 it and do the analytics within those two months; is that
:52:05 correct?
:52:05 A. That's correct.
:52:06 Q. And concerning the amount of time to develop a
:52:12 lyophilized product, are you aware that Cephalon's
:52:16 lawyers argued in their opening statements that Mr. Brittain
:52:19 started to develop the lyophilized form of Treanda in
:52:24 early of February 2004 and then was done by April 15th of
:52:31 2004?
:52:31 A. I do not recall this exact date because I did not
:52:35 concentrate on these statements at all because I was asked
:52:39 to form my opinion as the eyes of the POSA before 2005. So
:52:44 I take this into account, but I do not recall having studied
:52:49 that document.
:52:50 Q. Now, Doctor, you understand that some of the patent
:52:58 claims in this case require certain limitations on the
:53:02 amounts of bendamustine ethylester that can be present in
:53:06 the claimed invention; is that correct?
:53:08 A. I understand that, yes.
:53:09 Q. And you understand the bendamustine ethylester is
:53:13 sometimes referred to as BM1EE; isn't that correct?
:53:16 A. Yes.
:53:17 Q. Now, Doctor, you personally don't know if BM1EE could

form as a degradant of bendamustine without ethanol also being present; is that correct?

A. We learned that it's a precursor of the synthesis, so this we know, but that it can form from hypothetically pure bendamustine without the presence of ethanol? As being not a synthetic chemist, I, in fact, agree, I do not know in details. It could theoretically form in other pathways, I assume, but I really do not know.

Q. Doctor, I want to talk about the ready-to-use liquid injectable solutions of bendamustine now.

You were not aware of any liquid injectable solutions of bendamustine that were commercially produced anywhere in the world between 1983 and 2005; is that right?

A. No.

Q. So when you say no, that means in our not aware of any?

A. No, I was not aware of any.

Q. Doctor, this morning you testified that you conducted an obviousness analysis of the relevant patent claims; is that correct?

A. Yes.

Q. Do you have understanding that absolute predictability is required to find obviousness?

A. Absolute predictability? I have not heard that

definition.
Q. And what is your understanding in your analysis of what kind of predictability is required to find obviousness?
A. In my opinion, it is a very high probability of success that leads to obviousness; which is somehow different from absolute.
Q. All right. Now, Doctor, you recall earlier today you had some slides discussing the sink conditions of the Ribomustin?
A. I recall that, yes.
Q. Now, you're not aware of the numerical sink conditions that are actually associated with the Ribomustin reconstitution solution; is that correct?
A. I could calculate those conditions. I would like to.
Q. But you didn't do that in your expert report; is that correct?
A. No, I did not recall having done so.
Q. And your expert report also does not report on the equilibrium solubility threshold of Ribomustin; is that correct?
A. No, my expert report does not refer to that number.
Q. So you would agree that a person of ordinary skill in the art could conduct solubility studies to determine the

:56:42 **sink conditions and the equilibrium solubility thresholds of**
:56:47 **a molecule; is that correct?**
:56:50 A. **Absolutely, I agree that a person can do this.**
:56:53 Q. **All right. Doctor, can you please look at DTX-581-A**
:57:01 **in your exhibit binder.**
:57:11 A. **I have it.**
:57:12 Q. **And do you recognize that as the Lyondell paper you**
:57:18 **spoke about earlier in your testimony?**
:57:20 A. **Yes, it's the Lyondell paper.**
:57:22 Q. **And just for the record, this is the 581-B version of**
:57:28 **the same document. It's even a clearer copy than was**
:57:32 **previously used in this case.**
:57:34 **Now, Doctor, you understand this is a marketing**
:57:44 **brochure that's designed to sell TBA to formulators; is that**
:57:48 **right?**
:57:48 A. **That's right.**
:57:52 Q. **And if you look at the last page of this reference --**
:58:03 A. **Yes.**
:58:03 Q. **-- at the very bottom left-hand corner, do you see**
:58:07 **that there is a copyright date of 2003?**
:58:10 A. **Yes, I see that.**
:58:14 Q. **And on that same page, do you see that the Lyondell**
:58:19 **company had offices all over the world?**
:58:23 A. **I see this.**
:58:29 Q. **And those cities include Houston, the Netherlands,**

:58:33 **Hong Kong, Newtown Square, Pennsylvania, and San Paulo, Brazil?**

:58:40 A. **I can read that, yes.**

:58:41 Q. **And in reviewing this Lyondell document, Doctor, you would agree that the document reports that various large pharmaceutical companies have used TBA in developing their products; is that correct?**

:58:43 A. **They have used TBA for different purposes. Whether it's in development product, they include market. Have to be very cautious to agree to that. But in certain cases, I agree, but not in all of those cases for where reference has been made have products been developed.**

:58:52 Q. **Let's look at Page 16, DTX-581B.0016.**

:58:58 **There is a paragraph entitled Freeze-Drying of Water-Unstable Drugs.**

:59:04 **Do you see that?**

:59:05 A. **Yes, I see that.**

:59:12 Q. **And do you see that the Lyondell reference reports that the Upjohn Company used TBA? Correct?**

:59:18 A. **Yes, I see that.**

:59:20 Q. **The second sentence of that says, "Lyophilization of a buffered lactose formulation of PGE-1 from a tertiary-butyl alcohol (TBA) - water mixture provides superior product stability than when freeze-drying from a 100-percent aqueous system."**

:59:22

:59:23

:59:26

:59:27

:59:29

:59:34

:59:42

:59:42

:59:45

:59:50

:59:55

:00:01

:00:09 A. **I read that, yes.**

:00:10 Q. **If you turn to the previous page, Page 15, do you see**
:00:13 **that?**

:00:15 A. **Yes, of course.**

:00:16 Q. **Do you see the first paragraph on Page 15 reports that**
:00:22 **Shionogi and company has reported a process that uses**
:00:26 **aqueous TBA, the first sentence?**

:00:33 A. **I can read that, yes.**

:00:35 Q. **The previous page to that, Page 14, DTX-581B.0014, the**
:00:46 **second full paragraph, first sentence, Ciba-Geigy reported**
:00:52 **using TBA and N-methyl pyrrolidone as a water miscible**
:01:00 **organic solvents."**

:01:04 **Correct?**

:01:05 A. **Yes, I read that.**

:01:06 Q. **And if we look at Page 9 of this document, there is a**
:01:27 **paragraph that begins with the phrase "TBA as Mass Transfer**
:01:33 **Accelerant. The first sentence says, "Literature shows that**
:01:36 **Beecham Pharmaceuticals has extensively studied the effect**
:01:40 **of organic solvents, especially TBA, on freeze-drying**
:01:44 **efficiency and product properties."**

:01:46 **Correct?**

:01:47 A. **Correct.**

:01:48 Q. **Do you understand that Beecham Pharmaceuticals turned**
:01:53 **into Smithkline Beecham Pharmaceutical Company?**

:01:57 A. **Yes, sir.**

:01:57 Q. **And that company turned into GlaxoSmithKline.**
:02:01 **Correct?**
:02:01 A. **Yes.**
:02:01 Q. **And looking at Page 3 of the Lyondell reference, in**
:02:10 **the circle at the top of the page, it discusses physical**
:02:21 **attributes of TBA. Correct?**
:02:25 A. **Yes.**
:02:26 Q. **And those attributes include high melting point.**
:02:30 **Correct?**
:02:30 A. **Yes.**
:02:30 Q. **Easy crystallization. Correct?**
:02:33 A. **Yes.**
:02:34 Q. **High vapor pressure. Correct?**
:02:36 A. **Yes.**
:02:36 Q. **Easy sublimation. Correct?**
:02:39 A. **Yes. I can read that.**
:02:41 Q. **And, Doctor, if you go to the second-to-last page of**
:02:53 **the Lyondell reference, do you see that the Lyondell paper**
:03:07 **is supported by at least 23 scientific references?**
:03:16 A. **I see this.**
:03:18 Q. **And do you recognize the names of any of those**
:03:25 **references, or any of those authors in those articles?**
:03:30 A. **Of course, I do. Shall I comment?**
:03:37 Q. **Which names do you recognize that you have learned**
:03:39 **from your experience?**

:03:42 A. **Maybe we take Teagarden first, because you just**
:03:46 **pointed out this reference in the context of this**
:03:56 **alprostadil product before. This is in fact I think the**
:03:58 **reference that goes to this Caverject product we discussed**
:04:02 **before.**
:04:04 **I recognize Peter Von Hoogevest, whom I know**
:04:10 **personally, about his liposome stuff you just described**
:04:14 **before. But I am quite sure that this stuff has not seen**
:04:22 **the market.**
:04:24 **I recognize a lot of other colleagues. Some of**
:04:29 **them I know personally. Some not. But what I don't recall**
:04:36 **is these other examples you have made have ended up in**
:04:39 **products.**
:04:42 Q. **And Reference 1E is a reference to Louis Rey.**
:04:50 **Correct?**
:04:50 A. **Yes.**
:04:50 Q. **And Reference 7 is reference to Baldi. Correct?**
:04:56 A. **Yes.**
:04:57 Q. **And Reference 22 is a reference to a DeLuca. Correct?**
:05:02 A. **Yes.**
:05:02 Q. **Do you know DeLuca?**
:05:04 A. **I don't know him personally. But I know who he is. I**
:05:08 **am not sure whether he is still alive, but I know who he**
:05:22 **was.**
:05:22 **MR. CWIK: Thank you, Doctor. No further**

questions.

THE COURT: All right. Redirect.

MR. MITROKOSTAS: No redirect, thank you.

THE COURT: Doctor, thank you very much.

THE WITNESS: Thank you.

THE COURT: Safe travels home. Be careful getting down.

(Witness excused.)

MR. WARE: Your Honor, at this time Cephalon calls Henry Grabowski, an economist from Duke, with respect to some of the economic issues in the case, including commercial success.

... HENRY G. GRABOWSKI, having been duly sworn as a witness, was examined and testified as follows ...

THE COURT: Good afternoon.

THE WITNESS: Hello, Your Honor.

DIRECT EXAMINATION

BY MR. WARE:

Q. Dr. Grabowski, again, please, state your name for us?

A. Henry George Grabowski.

Q. How are you currently employed, Dr. Grabowski?

A. I am employed at Duke University. I am Professor Emeritus. And I am also director of the program in pharmaceuticals and health economics.

Q. How long have you been on the faculty or were you on

:07:41 **the faculty at Duke University?**
:07:43 A. **I have been there since 1972.**
:07:45 Q. **Can you give us a little bit of your academic**
:07:49 **background, beginning with college, and take us through your**
:07:52 **formal educational career?**
:07:54 A. **Yes. I received a Bachelor's of science from Lehigh**
:07:59 **University in 1962 in engineering physics. Then I received**
:08:04 **my Master's and Ph.D. from Princeton University in**
:08:10 **economics. That was, the Ph.D. was in 1967.**
:08:14 Q. **Can you tell us what the focus of your research has**
:08:19 **been as it may relate to your testimony here today?**
:08:22 A. **Well, most of my work has been in the health care**
:08:25 **sector, and with a particular focus on innovation,**
:08:30 **competition, and regulation in the pharmaceutical industry.**
:08:33 Q. **Have you published in that area, including articles**
:08:38 **and other publications, over time?**
:08:41 A. **Yes. I have published more than a hundred**
:08:43 **peer-reviewed articles and several books on the economics of**
:08:49 **the pharmaceutical industry.**
:08:49 Q. **While we are on that subject, let me ask you to take a**
:08:52 **look at PTX-254, which I believe to be a relatively current**
:08:58 **version of your curriculum vitae. Could you verify that for**
:09:04 **us?**
:09:05 A. **Yes.**
:09:08 Q. **And your publications are listed several pages into**

:09:12 **the CV, are they not?**

:09:13 A. **Yes, they are.**

:09:14 Q. **And are there any particular publications or papers**

:09:19 **which may have relevance to some of the discussion you will**

:09:22 **have with us today?**

:09:24 A. **Well, one I would point out, on Page 10, sort of down**

:09:32 **towards the bottom of the page, is called "The Economics of**

:09:34 **New Oncology Drug Development." That was with my colleague,**

:09:38 **Joseph DiMasi. It was published in the Journal of Clinical**

:09:44 **Oncology.**

:09:44 Q. **What was the nature of that paper, the substance of**

:09:48 **that paper?**

:09:49 A. **Well, oncology drug development had a big increase in**

:09:55 **investment and new drug introductions beginning, I'd say, in**

:10:00 **the middle nineties. Prior to that time, the biggest areas**

:10:05 **of research were more cardiovascular, anti-infectant and**

:10:10 **CNS.**

:10:12 **But oncology drug development really went**

:10:17 **forward in this period. And there were many new drugs,**

:10:23 **several of which got priority review at the FDA, indicating**

:10:28 **a significant advance. And many of them were directed**

:10:32 **towards relatively rare cancers, those that would be**

:10:37 **considered Orphan Drugs.**

:10:38 Q. **Have you also been the recipient over time of grants**

:10:43 **from institutions, including the National Science**

Foundation?

A. **Yes. Our program at Duke has had a series of grants from the National Science Foundation to look at how FDA regulation is affecting the industry. We have also looked at competition. We have looked at marketing and pricing of pharmaceuticals.**

So we have received grants to look at various competitive and regulatory issues.

Q. **Have you had a role in health reform legislation over time, including the Affordable Care Act and any of its precursors?**

A. **Yes. I have been asked to testify on our research several times in front of Congress, including before the Hatch-Waxman was passed, and then on its anniversaries, and also most recently was when the Affordable Care Act was being passed and the drug aspects of that act.**

Q. **Have you also been a consultant to certain government agencies, including the Institute of Medicine of the National Academy of Sciences and various other entities?**

A. **Yes. Our program has done projects for several agencies, including the General Accounting Office, and Congressional Budget Office, and some of the other ones you mentioned.**

Q. **Have you also had occasion to serve as a visiting scholar to international institutions of some renown?**

:12:23 A. **Yes. I was visiting scholar at the Institute of**
:12:28 **Management in Berlin, the Office of Health Economics in**
:12:31 **London, and the Center for Medicine Research in London.**
:12:37 Q. **For some period of time during your distinguished**
:12:40 **career, you had occasion to serve on the board of directors**
:12:41 **of a pharmaceutical company, did you not?**
:12:44 A. **Yes. It was a development stage company, Triangle**
:12:50 **Pharmaceuticals, located in Durham. And I was on their**
:12:52 **board of directors. It was focused on antiviral and**
:13:00 **anti-AIDS drugs. One of our drugs is part of the leading**
:13:04 **triple therapy for AIDS.**
:13:05 Q. **Apart from that connection with the pharmaceutical**
:13:09 **industry, have you also had occasion to consult for and work**
:13:12 **with a number of major U.S. and foreign pharmaceutical**
:13:17 **companies?**
:13:18 A. **Yes. I have been an advisor on strategic issues to**
:13:22 **several companies, Merck, Pfizer, Sandoz, Allergan, others.**
:13:27 Q. **Has your work been relied upon by certain**
:13:35 **Congressional entities or the Congressional Budget Office,**
:13:39 **among others, with respect to drug price competition?**
:13:43 A. **Yes. We have done some work for the Congress budget**
:13:49 **office and some others.**
:13:51 Q. **I don't know if I asked you, is the CV that I have**
:13:54 **placed before you, PTX-254, a relatively current version of**
:13:58 **your curriculum vitae?**

A. **Yes, it is.**

MR. WARE: Your Honor, at this time I offer Dr. Grabowski as an expert economist on the issue in this case of commercial success and related pharmaceutical industry issues, including FDA practice.

THE COURT: Okay. Any objection?

MS. HORTON: I guess I would have no objection to the first part. But to the FDA practice point, that is not something that has been disclosed or discussed before.

MR. WARE: I overstated that. There may be tangential questions with respect to FDA, for example, the Orphan Drug exemption letter, as to which he has specifically published.

THE COURT: You are not offering him as an expert on FDA matters.

MR. WARE: I am not.

MS. HORTON: No objection.

THE COURT: The Doctor is accepted as an expert in this field.

MR. WARE: Thank you, Your Honor.

BY MR. WARE:

Q. **Can you tell us, Dr. Grabowski, what you were asked to do in this matter on behalf of Cephalon?**

A. **Yes. I was asked to evaluate whether Treanda was a commercial success, and if so, whether there was a nexus to**

:14:59 **the patents at issue.**

:15:00 Q. **Broadly speaking, what's your understanding of the**

:15:03 **subject matter of the four patents at issue in this case?**

:15:08 A. **Well, they deal with drug formulation, and they deal**

:15:13 **with excipients in that formulation that improved purity,**

:15:20 **and, as shown on the demonstrative, they involve both the**

:15:25 **bulk solution, the lyophilized composition, and the**

:15:28 **reconstituted solution. And they also involve the use of**

:15:33 **this formulation for CLL and NHL.**

:15:37 Q. **Have you been advised of a stipulation among the**

:15:40 **parties that, in fact, a commercial embodiment of those**

:15:45 **inventions is Treanda?**

:15:47 A. **Yes.**

:15:47 Q. **Now, are you aware that bendamustine hydrochloride as**

:15:55 **developed by Cephalon and Salmedix had previously been used**

:16:00 **in Europe?**

:16:02 A. **Yes, I believe it was first used in East Germany,**

:16:06 **going back to the 1970s.**

:16:08 Q. **So far as you know, at any point prior to the point at**

:16:16 **which Treanda was approved by the FDA, had any bendamustine**

:16:23 **hydrochloride formulation been approved for use in the**

:16:26 **United States by the Food and Drug Administration?**

:16:30 A. **No. My understanding is that was the first approval.**

:16:33 Q. **Let me direct your attention to PTX-285, a letter from**

:16:38 **the FDA. And I ask you whether you recognize this?**

A. **Yes.**
Q. **Just tell us what it is.**
A. **Basically, this is a letter to Cephalon indicating that their NDA had been approved for the use in chronic lymphocytic leukemia, CLL. And this is the formal approval letter.**
Q. **When the letter speaks to its approving Treanda, is that coextensive with saying it's approving bendamustine hydrochloride, if you know?**
A. **No, because the FDA does not approve an active ingredient, a moiety. What it approves is a drug formulation, which is Treanda.**
So bendamustine is the active ingredient in the Treanda formulation. But what's being approved is the formulation.
Q. **Am I correct, based on the date we see in the lower right corner here, that the approval date was March 20, 2008?**
A. **Yes.**
Q. **Let me direct you to a similar letter with respect to NHL and ask you if you recognize this. That is Exhibit 328?**
A. **Yes.**
Q. **And is that a similar letter approving Treanda, except for the indication of NHL?**
A. **That's correct.**

:18:27 Q. **What is the date of this approval?**

:18:30 A. **This is October 31st, 2008.**

:18:39 Q. **Based on your knowledge, in the course of approval of pharmaceutical compounds, does the FDA distinguish between the formulation and the active pharmaceutical ingredient?**

:18:56 **MS. HORTON: Objection, Your Honor. I am not sure this is disclosed anywhere in his expert report.**

:19:02 **THE COURT: Is this the tangential type of FDA testimony?**

:19:08 **MR. WARE: Yes.**

:19:08 **THE COURT: What was the question again, Mr. Ware?**

:19:10 **MR. WARE: I really asked whether or not, in the course of approval, the FDA distinguishes between the API and the formulation.**

:19:17 **THE COURT: He has already answered it, quite frankly, on the previous question. I will let him answer it again.**

:19:24 **Go ahead.**

:19:26 **THE WITNESS: Yes. You know, it clearly is concerned with the active ingredient. But it approves the formulation of that active ingredient.**

:19:33 **BY MR. WARE:**

:19:37 Q. **Do you understand -- well, let me put it a little differently. Assuming here that the defendants argue that**

:19:48 **the success of Treanda is related not to the formulation**
:19:55 **that includes bendamustine hydrochloride but effectively to**
:19:59 **bendamustine hydrochloride itself, do you have an opinion on**
:20:03 **that matter?**
:20:05 A. **Yes. I think they are both very important. Clearly,**
:20:09 **you need an active ingredient to attack the cancer cells.**
:20:13 **But you also need a product that the FDA deems is accepted**
:20:20 **for purity standards, meets its purity standards and is**
:20:24 **stable.**
:20:26 **So without an approvable formulation, you can't**
:20:32 **realize the benefits of the active ingredient. So they are**
:20:36 **both necessary and important.**
:20:38 Q. **For purposes of your testimony here today, have you**
:20:42 **read the expert report of the expert on behalf of defendants**
:20:47 **whom we anticipate will be called tomorrow, that is, Dr.**
:20:52 **Hofmann?**
:20:52 A. **Yes. Mr. Hofmann, yes.**
:20:54 Q. **Mr. Hofmann.**
:20:56 **And assuming that among the arguments Mr.**
:20:59 **Hofmann will make is that you should somehow have allocated**
:21:04 **some portion of commercial success among individual claims**
:21:08 **of the patents and/or among the patents themselves, do you**
:21:13 **agree that that is an appropriate analysis from an economic**
:21:17 **viewpoint?**
:21:18 A. **You mean among the different claims of the patents?**

Q. **Yes.**

A. **No, I don't think that is a meaningful exercise in the sense that they all relate to purity and stability as a family and reconstitution. They are all part of what provides benefits to patients and to practitioners. I am not even sure how you would allocate among the different -- what methodology you could use.**

I don't think it's a meaningful exercise.

Q. **For purposes of your analysis, did you become familiar to some degree with the indications for Treanda, including CLL and indolent NHL?**

A. **Yes, I did.**

Q. **And with respect to those indications, can you tell us, give us an overview of the CLL indication on which you relied?**

A. **Yes. CLL is a very serious, life-threatening disease. It affects less than 200,000 patients, so it's eligible for an Orphan indication. And I think I remember that there is about 5,000 deaths per year from CLL.**

Q. **Can you basically describe your understanding of indolent NHL and the extent of that affliction in the United States?**

A. **Well, it's also a very serious cancer. It's a more prevalent cancer. It affects elderly people disproportionately. So it's an important disease to try to**

develop new therapies for.

Q. For purposes of your analysis, are there, and did you use, objective indicia of the question of whether there was a long-felt unmet need for a drug like Treanda and a formulation that's the subject of the patents?

MS. HORTON: I would object as duplicative to Dr. Leonard's testimony, who we heard last week on the same subject.

THE COURT: Mr. Ware.

MR. WARE: It may duplicate something. I think it's part of the basis of his opinion. He has addressed that from the beginning. It's disclosed in his report.

THE COURT: I will let you go forward as long as you make the representation to the Court that we are not running afoul of my dictates on cumulative testimony.

MR. WARE: I make that representation. If I skirt any closer, I will stop.

THE COURT: You should rise and object again, counsel.

I will overrule it for now.

BY MR. WARE:

Q. My question is, any indicia that you looked at for purposes of making such a determination?

A. Yes. I prepared a slide or roadmap here, but the focus of my analysis of commercial success is on dollar

:24:39 **sales and unit sales and patient penetration, which is a**
:24:44 **form of market share.**
:24:46 Q. **Will you tell us, taking those one by one, what**
:24:51 **analysis you made with respect to dollar sales and what**
:24:54 **inferences you drew or conclusions you drew as a result?**
:24:58 A. **Yes. Basically, I looked at the IMS data on dollar**
:25:04 **sales. IMS is a leading purveyor of data to the**
:25:08 **pharmaceutical industry and it's used more broadly.**
:25:13 **I prepared some tables and graphs in that**
:25:18 **regard.**
:25:18 Q. **Okay. Before we get to those, did you make a**
:25:21 **determination of the aggregate net sales of Treanda over**
:25:26 **time?**
:25:26 A. **Yes, I did. They were effectively, I think, 3 billion**
:25:33 **dollars.**
:25:33 Q. **And you indicated that the data that you derived these**
:25:37 **figures from was IMS data. Is that correct?**
:25:41 A. **Yes.**
:25:41 Q. **Let me direct your attention to a table and ask you**
:25:46 **whether or not this is something prepared by you or at your**
:25:50 **direction and labeled PDX-11-7?**
:25:53 A. **Yes, it is.**
:25:54 Q. **Tell us what this is telling us and how it was**
:26:00 **meaningful to your opinions?**
:26:02 A. **Yes. So this is the annualized dollar sales. The**

product was introduced in the second quarter of 2008. I examined it through the third quarter of 2014. One can see sales in the first year were 68 million, and then they grew rapidly to over 200 million, then almost 400 million. And by 2013, they were just under 700 million.

And it stops at the end of the third quarter in 2014, because that's when the lyophilized product was essentially changed to a liquid form by Cephalon.

Q. If I may direct you to another chart marked PDX-11-8, is this likewise a chart prepared at your direction?

A. Yes. This is essentially the same data, but displayed quarterly. So one can see the trends over time. And there is a very sharp upward acceptance of the product, an increase in dollar sales from, in the first quarter, less than ten million, or ten million or so, and then by 2014, it was close to 180 each quarter.

MS. HORTON: Your Honor, I note for Your Honor that this is all stuff that we have gone over with Mr. Rainey last week on Tuesday. Just to get the duplicate --

THE COURT: I do recall seeing this graph.

MR. WARE: You saw this graph. You don't have any background on it, except that sales from an internal point of view were at this level. To that extent --

THE COURT: Fair enough.

MR. WARE: This is an economic analysis of this

:27:54 **data.**

:27:55 **THE COURT: I think that's a fair**

:27:56 **characterization. I will overrule the objection.**

:28:15 **BY MR. WARE:**

:28:24 Q. **You said or referred to widespread or rapid**

:28:29 **acceptance. By whom, to your understanding, was the drug**

:28:33 **Treanda accepted in the marketplace?**

:28:38 A. **That was by practitioners. There's another slide**

:28:41 **about, showing vials, which also shows acceptance of units,**

:28:46 **and that's also reflected in the dollar sales.**

:28:50 **And I think the rapid acceptance is, you**

:28:55 **know, reflective of what Dr. Leonard said of an unmet need**

:29:01 **at the time of its introduction, its rapid penetration of**

:29:06 **the market.**

:29:06 Q. **Did you also examine the number of units out the door**

:29:11 **as opposed to dollars in?**

:29:13 A. **Yes, I did.**

:29:14 Q. **And let me ask you to look at PDX 11-9 and tell us how**

:29:19 **this relates to your economic evaluation of commercial**

:29:24 **success.**

:29:24 A. **Well, this is looking at it from the number of vials**

:29:28 **that are shown, and they also had a very similar upward**

:29:33 **trend as dollar sales, and starting from, you know, under**

:29:41 **20,000 unit vials sold in the early 2008 to well over**

:29:50 **100,000 by 2014.**

:29:53 Q. **In your original summary slide you mentioned patient**
:29:59 **penetration and market share in quotes. Tell us what that**
:30:03 **is, if you would, please.**
:30:04 A. **Basically, I looked at data from a company called**
:30:09 **Tandem and looked at the usage of different regimens to**
:30:17 **treat both CLL and NHL, and Tandem is another audit source.**
:30:24 **They look at data, patient utilization data on a very**
:30:29 **detailed level.**
:30:30 Q. **When you talk about regimens, can you tell us what**
:30:33 **that term means?**
:30:34 A. **Well, cancer drugs are often used in combination.**
:30:39 **They can be a monotherapy, but more often, they're a, you**
:30:43 **know, a combination of several therapies at once. So it's**
:30:48 **appropriate to look at individual regimens. In fact, for a**
:30:53 **drug like CLL, there's more than 160 different regimens that**
:30:59 **doctors can choose from.**
:31:00 Q. **How did you determine or assure yourself that the**
:31:04 **regimens which you considered were the appropriate regimens**
:31:08 **for purposes of analyzing the question of commercial success**
:31:11 **of Treanda?**
:31:12 A. **Well, I relied on Dr. Leonard, who sort of grouped the**
:31:19 **regimens into therapeutic alternatives. Dr. Leonard focused**
:31:26 **on the way a physician would look at what the alternatives**
:31:33 **were to treat CLL, and these are the regimens he put forth.**
:31:43 **Some of them are mono, like Rituxan and Leukeran, but more**

:31:48 **often they're broad regimens like Fludarabine was a regimen**
:31:54 **and widely in use when Treanda was used, and Fludarabine**
:32:01 **would be the principal drug, but it would typically be used**
:32:03 **with other drugs, generally with Treanda.**
:32:07 **So these were the seven groupings or**
:32:10 **groupings of therapeutic regimens that he indicated. And**
:32:13 **then I checked that with the Tandem data, to see if these**
:32:17 **were the most prevalent regimens used, and every year that I**
:32:22 **analyzed, these were more than 80 percent of the regimens.**
:32:24 **These 160 regimens boiled down to these therapeutic**
:32:30 **alternatives, so I felt that was a meaningful way to analyze**
:32:34 **the treatment regimens.**
:32:36 Q. **The regimens to which you are speaking now and the**
:32:38 **therapeutic alternatives are set forth, are they not, in**
:32:42 **PDX-11-10, a slide entitled "CLL patient penetration." Is**
:32:48 **that right?**
:32:48 A. **Yes, that's right.**
:32:50 Q. **And that is what you have been referring to in the**
:32:53 **last couple of minutes?**
:32:54 A. **Yes, I have.**
:32:55 Q. **Now, in the left-hand column, you indicated that these**
:32:57 **are seven, the seven principle regimens of the 160; is that**
:33:01 **correct?**
:33:01 A. **Yes.**
:33:01 Q. **And let me ask you. If we fill in some data, is there**

:33:07 additional information that you reviewed that was
:33:10 significant to you in forming your opinion?
:33:12 A. Yes. Well, you can see that when Treanda was
:33:16 introduced, Fludarabine regimens are the primary drugs being
:33:22 used. They had just around 50 percent of the total
:33:25 regimens. And Treanda in its first year had ten percent.
:33:30 Rituxan had ten percent. Leukeran 11 percent, Leukeran mono
:33:37 and Rituxan mono. But then as you see over time, there was
:33:41 a rapid growth in the Treanda regimens from ten percent
:33:45 upwards, so that by 2013, Treanda had 40 percent of the
:33:51 regimens. That was the most utilized regimens for CLL
:33:56 followed by Fludarabine and there were some new regimens
:34:00 coming into existence that gained shares in 2013 and '14.
:34:05 Q. All right. Let me direct you to an additional chart,
:34:10 if I may, marked PDX-11-12, also entitled CLL, patient
:34:17 penetration.
:34:17 Is this another way of looking at Treanda's
:34:20 growth over time against other drugs?
:34:24 A. Yes. This is essentially a monthly moving average.
:34:31 It shows the trend over time and the big red line is Treanda
:34:35 regimens, and you can see just what I had previously
:34:38 indicated, Treanda started with ten percent, Fludarabine
:34:46 50 percent. Over time, Treanda's growth increased and
:34:51 peaked around the middle of 2014 at 40 percent.
:34:56 Q. The top green line, however difficult to read, is a

:35:00 **Fludarabine regimen?**

:35:04 A. **Yes, regimen.**

:35:05 Q. **And as Treanda is ascending, that appears to be descending?**

:35:10 A. **Yes, that's correct.**

:35:11 Q. **Is that consistent with the data you reviewed?**

:35:14 A. **Yes, it is.**

:35:15 Q. **Let me ask you to look at another slide or perhaps can we take a look at a breakdown of regimens if you were to focus on the top five regimens and tell us what that might look like, referring you specifically to PDX 11-13 entitled "Top five regimens and CLL."**

:35:40 A. **Yes. So this is looking at individual regimens and the top five, and it shows that two of the top five were Treanda regimens, either Treanda and mono by itself or Treanda with Rituxan, and so this is also confirmatory that Treanda was a leading product and, in fact, was two of the top three regimens utilized over this whole period of 2008 to 2014.**

:36:12 Q. **Treanda mono means used on its own by itself, is that correct, as a therapy?**

:36:19 A. **Yes.**

:36:19 Q. **And directing you to the blue line labeled FCR, can you just identify what that is?**

:36:24 A. **That is a cocktail. R is Rituxan and, you know, I**

:36:33 **think F is Fludarabine. I am not sure what the C is.**

:36:37 Q. **Let me direct you, you've been talking about CLL**

:36:40 **regimens, have you not?**

:36:41 A. **Yes.**

:36:42 Q. **Let me direct you to indolent non-Hodgkin's lymphoma,**

:36:47 **and specifically the slide 11-14, and ask you whether or not**

:36:50 **you did a similar analysis of the principal cocktails as you**

:36:55 **put it or regimens applicable to NHL.**

:36:59 A. **Yes. And this, once again, I've relied on Dr. Leonard**

:37:03 **to outline what the therapeutic alternatives or groupings of**

:37:08 **regimens were, and these were the ones he outlined or**

:37:17 **indicated these were the choices that physicians would use,**

:37:21 **including Fludarabine regimens and Treanda regimens and**

:37:26 **Rituxan, but also some regimens or cocktails like CVP-R**

:37:42 **instead of Rituxan, Prednisone-type regimen. And CHOP-R**

:37:52 **involves another drug.**

:37:52 **So these were the alternatives he outlined.**

:37:55 **And, once again, I checked that they would be in the Tandem**

:37:58 **data that they were the prevalent regimens and accounted for**

:38:01 **the majority of the usage.**

:38:02 Q. **And without going through it in detail, the bottom**

:38:07 **highlighted line here shows the growth of Treanda regimens**

:38:10 **over time with respect to the NHL patient penetration; is**

:38:14 **that correct?**

:38:14 A. **Yes.**

:38:14 Q. **Now, when you talk about patient penetration, what is**
:38:18 **that actually measuring?**
:38:19 A. **Basically, there's these 160 regimens or over 100**
:38:24 **regimens in the case of NHL, and what this is measuring is**
:38:30 **how many patients in a particular period in a particular**
:38:35 **year, this is a moving average, would be on a Treanda**
:38:40 **regimen or a Fludarabine regimen. And in this case, I'm**
:38:48 **looking at penetration second or higher lines of indolent**
:38:56 **NHL treatment, because that's what Treanda is indicated for.**
:39:01 **It's indicated for use by patients who are**
:39:05 **refractory to a Rituxan or a Rituxan regimen, and that is**
:39:14 **often the prevalent first line therapies, and these are the,**
:39:19 **what could be used as second line therapies. And one sees**
:39:25 **that Treanda has come to be over 50 percent of those**
:39:28 **regimens.**
:39:29 Q. **When we look at these percentages here, these are**
:39:33 **percentages of patients who used the regimen in a given**
:39:36 **year; is that correct?**
:39:37 A. **Yes.**
:39:38 Q. **All right. Now let me direct you -- let's skip 16 and**
:39:46 **go to patient penetration, all lines NHL, which is**
:39:51 **PDX-11-17.**
:39:54 **You were talking a moment ago about second or**
:39:58 **higher lines of treatment for iNHL. What are we looking at**
:40:03 **here when it says "all lines"?**

A. **Well, this is looking at all lines of therapy, including first line therapy for NHL, and for all types of NHL.**

Q. **And from an economic viewpoint, is there any significance to whether a physician prescribes Treanda within its specific FDA approved indication or so-called off label?**

A. **Well, in cancer, there is lots of experimental use, both on label and off label, to see what works for the patient, both in mono and combination therapy. So this is very common.**

And what this indicates is that Treanda is also being used first line in many cases because it's useful first line therapy as well even though it's not -- it's a so-called off label use of it. And that's not uncommon in oncology.

And from a commercial success standpoint, I think it also, the patent claims are, for the formulation, the use of NHL when it's on label or off label. So I think it is -- this indicates that it's a useful therapy for all lines of NHL.

Q. **Let me ask you to talk for a few minutes about the relationship between the success, financial success as you've described it and the patents-in-suit.**

You're familiar, are you not, with the term

nexus?

A. **Yes.**

Q. **And you are familiar in general with the legal construct that the patented invention has to be connected to the success you're talking about?**

Do you understand that?

A. **Yes.**

Q. **Now, what characteristics of Treanda resulted from the patents-in-suit as you understand it?**

A. **Well, the patents-in-suit were connected to purity and stability, and I think they were important in FDA acceptance or approval. They were important in terms of manufacturing scaleability, and they were important in terms of the use in the clinic, the reconstitution of this lyophilized formulation.**

Q. **For purposes of your determination whether or not there is a nexus, have you evaluated certain characteristics as exemplified on PDX 11-18?**

A. **Yes. These relate to both experts that I've relied upon determining a nexus, and it's consistent with my economic analysis, and then also other factors that I looked at, like the roles, the role of marketing and promotion, the role of the licensing agreement, and the role of orphan drug status.**

Q. **Have you had occasion to review the trial testimony of**

:43:25 **Mr. Rainey, the head of sales of Cephalon, and Drs. Leonard,**
:43:31 **Ippoliti and Glick?**
:43:34 A. **Yes, I have.**
:43:35 Q. **Turning to your first bullet point, the experts, how**
:43:39 **do the opinions of Drs. Ippoliti and Leonard impact your**
:43:45 **expert analysis?**
:43:46 A. **Dr. Ippoliti spoke to the importance of reconstitution**
:43:50 **in the clinic, and that this is a product that can be**
:43:56 **reconstituted in a favorable way, and that it can be stored**
:44:02 **over a 24-hour period and that these were also important**
:44:07 **from a clinical standpoint.**
:44:09 **They provided values to patients and**
:44:13 **efficiencies in the hospital setting.**
:44:16 **Dr. Leonard, in addition to framing the analysis**
:44:20 **for my patient penetration, spoke to what was available as**
:44:27 **therapies as of 2005, that the existing therapies had**
:44:33 **problems either in efficacy or in terms of side effects, and**
:44:38 **that this, the introduction of the product, Treanda,**
:44:46 **addressed and provided an improvement, and so, you know, I**
:44:55 **think his analysis is basically unmet need, but it's**
:45:02 **consistent with my economic analysis of very rapid**
:45:07 **acceptance by physicians in the marketplace.**
:45:10 **So I think my economic analysis confirms his**
:45:15 **analysis that there was an unmet need and this was a product**
:45:19 **that was rapidly adopted and has maintained usage.**

:45:25 Q. **For purposes of your economic analysis, was there any**
:45:28 **significance to the fact that FDA granted this drug priority**
:45:33 **review?**
:45:33 A. **Yes. I think priority review is granted for products**
:45:39 **that are significant advances in terms of safety and**
:45:43 **efficacy, and that is also consistent with his**
:45:50 **characterization, that is Dr. Leonard's characterization of**
:45:54 **an unmet need that was fulfilled and rapid acceptance by**
:46:00 **physician.**
:46:02 Q. **Your second bullet point had to do with marketing.**
:46:05 **Did you take a look at marketing and promotion expenses and**
:46:08 **activities by Cephalon?**
:46:10 A. **Yes, I did.**
:46:13 Q. **Tell us what you considered and what observations you**
:46:17 **made in that respect.**
:46:19 A. **Well, essentially, I looked at data from IMS marketing**
:46:27 **and promotion to see the extent of marketing relative to**
:46:30 **sales. This is a frequently used metric and to look at the**
:46:37 **extent of marketing in a therapeutic product or a particular**
:46:42 **therapeutic area.**
:46:43 Q. **Directing your attention to the slide you see on the**
:46:47 **screen at the moment marked PDX 11-dash 8 -- 19? I can't**
:46:53 **read it. 19, can you tell us what this depicts and what**
:46:57 **significance it has to you and should have to us?**
:47:00 A. **Basically, it shows that there is relative to sales,**

very small levels of marketing for this product. It, from an IMS standpoint, marketing expenditures are relatively small, 3 million a year in the first year, first full year of marketing the product, and $119,000,000 in sales. So that's, you know, less than three percent and it's even lower percentages over time, which suggests to me that, you know, marketing is necessary to get out information to physicians, but it's not the key driver here of the experience with the product.

Q. Based on your experience, what is the key driver for physicians?

A. It's the safety and efficacy of the product in treating cancer and you have a stable and pure product that you can depend upon.

Q. Is there an average expenditure of advertising and promotion in pharmaceutical products, first year, second year, third year?

A. For products as a whole, I've done some work on that and, you know, as a general overview, it's like a hundred percent the first year, 50 percent the second year, and 25 percent the third year. This is a characteristic particularly of products that, you know, would be broadly used by GPs and you have hundreds of thousands of physicians.

Q. And apart from products generally, did you take a look

:48:40 1 **at products in this particular therapeutic space which might**
:48:45 2 **lend you some information?**
:48:47 3 A. **Yes. So I looked at other products that were**
:48:52 4 **evaluated as part of the therapeutic alternatives to Treanda**
:49:00 5 **and Fludarabine, Rituxan, and the other products listed**
:49:05 6 **here, going back to the first three years going, starting in**
:49:10 7 **the early 1990s to Fludarabine and whatever their**
:49:15 8 **introductory entry dates were, and you can see that in**
:49:19 9 **general, cancer drugs have much less marketing, which makes**
:49:24 10 **sense, because they're, they're being marketed to cancer**
:49:28 11 **oncologists and the important thing is to get out the**
:49:33 12 **information on clinical trials and you don't have to do the**
:49:37 13 **kind of marketing you do, say, for a lifestyle drug or a**
:49:43 14 **drug that's used more broadly by GPs. But even among these**
:49:49 15 **products that are competitors, Treanda is at the lower end**
:49:54 16 **of the spectrum, 2.6 percent in the first year, 1.2 percent**
:50:00 17 **in the second year, and less than one percent of marketing**
:50:04 18 **to sales.`**
:49:00 19 Q. **You have been referring in the last few moments to**
:49:47 20 **PDX-11-20. Is that correct ?**
:49:50 21 A. **Yes.**
:49:50 22 Q. **And that is entitled Marketing Expenditures Relative**
:49:54 23 **to Sales?**
:49:54 24 A. **Yes.**
:49:55 25 Q. **What conclusions did you draw with respect to the**

impact of marketing on the question of whether Treanda has been commercially successful?

A. Well, it's been commercially successful. But it's because it works very well as a treatment of CLL and NHL. And physicians have recognized that through experience and continued to use it. It's not a market-driven phenomenon.

Q. When you say a market-driven phenomenon, what do you mean by that?

A. Well, that, as I said, some marketing is useful and complementary, but if the product didn't work, you could market as much as you wanted but it wouldn't be used.

This isn't like a consumer product, like toothpaste or something.

Q. The third item you indicated that you looked at for purposes of this evaluation was the license agreement.

What was the competitive impact of that license agreement and its relevance to you in your analysis?

A. Well, I understand there was a licensing agreement from Fujisawa to Salmedix --

MS. HORTON: I note that wasn't disclosed as an exhibit that Dr. Grabowski was going to discuss or cited in his expert report.

THE COURT: Something was displayed?

MR. WARE: It was JTX-37, the cover page of the license agreement.

:51:31 **THE COURT: It was not?**

:51:32 **MS. HORTON: It was not disclosed per our**
:51:34 **pretrial agreement. So we didn't know he was going to be**
:51:36 **talking about it.**

:51:37 **THE COURT: Are you objecting to him discussing**
:51:39 **this?**

:51:39 **MS. HORTON: I guess I would be objecting along**
:51:42 **the lines that we discussed in our meet-and-confer last**
:51:45 **night. As long as Mr. Ware understands what our objections**
:51:49 **were there, we might not have an issue.**

:51:52 **MR. WARE: I don't understand those objections.**

:51:54 **THE COURT: Why don't you talk.**

:51:55 **MR. WARE: This was the subject of relatively**
:51:58 **extensive deposition testimony. I am not sure what the**
:52:00 **problem is.**

:52:02 **(Counsel confer.)**

:52:17 **BY MR. WARE:**

:52:19 Q. **One small controversy resolved.**

:52:23 **What, for your purposes, was the relevance of**
:52:26 **there having been a license agreement?**

:52:30 A. **Well, I think it provided some benefits to Salmedix.**
:52:33 **It provided some data and scientific information on bulk**
:52:38 **product. It was a starting point for an investigation into**
:52:41 **developing a product that was FDA approvable. But it was**
:52:45 **not a barrier to other firms investigating and doing this**

product.

As I indicated earlier, this product was available since the mid-seventies in Germany. So to the extent that other companies -- to the extent that other companies thought it was obvious or that it was obvious that -- to the extent it was obvious that this could be made into an FDA approvable product and there was a huge economic reward associated with it, other firms would have recognized that. They would have been motivated to pursue it.

Since the 1990s, firms have been facing shrinking sales, or replacement of the pipeline issues. So they are looking globally for new products.

So the fact that nobody pursued it over these four decades is to me an indication that it's not obvious, and the licensing agreement, while it had benefits, wasn't a barrier to other companies also pursuing this if it was a recognizable opportunity.

Q. The last of the four items of consideration you indicated was Orphan Drug status.

What importance did you attach to Treanda having been granted Orphan Drug status?

A. Well, I think that was granted when the product was approved in 2008. It was then, for the specific indication, first for CLL, then it got Orphan Drug status for NHL, which meant that other formulations of bendamustine couldn't be

approved for this product for seven years after it was introduced unless they were superior formulations.

But that was not a barrier. I think Mr. Hofmann said that was a barrier to other firms pursuing this project before in this case. But I don't see that -- it wasn't a barrier. It wasn't granted until 2008. And anybody was free to get that Orphan Drug approval if they pursued it. And they had an opportunity to do that for many years that this drug was on the market elsewhere in the globe.

Q. Let me direct you to Slide PDX-11-21, to an FDA letter of August 17, 2007. Can you tell us what this is? It is in your binder.

A. This is a letter from the FDA to Cephalon saying that they have received Orphan Drug designation on in June 2007 for bendamustine, trade name Treanda, for B-cell chronic lymphocytic leukemia, CLL.

Q. This document appears as Defendants' Exhibit 161 in your binder.

What is the significance, if any, of the language, quote, "Please be advised it is the active moiety of the drug and not the formulation of the drug that is designated"?

What does that mean?

A. Well, this is a designation to the active moiety bendamustine. But you don't get Orphan Drug exclusivity

:57:05 till you get an approval. And the approval which occurred
:57:10 in 2008 is for a particular formulation, the formulation
:57:17 that's Treanda.
:57:18 So basically, it's conveying an Orphan Drug
:57:22 designation to the product. But, in effect, the actual
:57:33 exclusivity attaches to the drug formulation that was
:57:37 approved in 2008.
:57:40 What this is saying is if you get approval and
:57:43 you are the first to do so, no other formulation, unless
:57:48 they are clinically superior, will have that designation.
:57:52 Q. Is this a broader protection or a narrower protection
:57:56 than if the protection itself had specifically been
:57:59 included?
:58:00 A. It's a broader formulation. It's what Congress
:58:03 intended to incentivize Orphan Drug approvals.
:58:10 Q. Based on your knowledge and understanding, is the FDA
:58:16 in this letter making any comment, qualitatively or in any
:58:21 other way, about the formulation itself?
:58:24 MS. HORTON: Objection, Your Honor. This is not
:58:29 in the expert report. This is relating to the tangential
:58:32 FDA issues we have been discussing. Dr. Glick was the
:58:36 expert on FDA issues, as I recall.
:58:38 THE COURT: Sustained.
:58:45 BY MR. WARE:
:58:45 Q. Have you reviewed the testimony of Mr. Rainey? I

:58:48 **think you said you did. Is that correct?**
:58:49 A. **Yes.**
:58:50 Q. **From an economic perspective and your analysis, what's**
:58:56 **the importance of the observations he made with respect to**
:59:00 **the particular formulation and the success of Treanda?**
:59:06 A. **Basically, I think he gave a company perspective that**
:59:10 **the product, that they investigated the product, they**
:59:16 **realized that -- the history of it, that the formulation was**
:59:21 **important in terms of its current acceptability, and that it**
:59:29 **is a commercial success from the standpoint of Cephalon.**
:59:34 Q. **You mentioned earlier that in the fourth quarter of**
:59:37 **2014 Cephalon introduced a liquid formulation. Is that**
:59:43 **correct?**
:59:43 A. **Yes.**
:59:43 Q. **In what way, if any, does that impact your view**
:59:48 **whether or not Treanda as a lyophilized composition was**
:59:53 **commercially successful?**
:59:55 A. **It doesn't change my opinion that the lyophilized**
:59:58 **product was a commercial success. As I indicated, it sold**
:00:03 **more than 3 billion dollars. And the liquid formulation is**
:00:12 **a line extension in pharmaceuticals. It represents an**
:00:17 **improvement at the usage stage, where you don't have to**
:00:20 **reconstitute the product. And that gives some advantage in**
:00:23 **the clinic.**
:00:23 **But basically, the success of the liquid product**

:00:30 **derives from the experiences with the lyophilized product**
:00:34 **and in no -- way it's come along in 2014, but there is a**
:00:44 **strong commercial success associated with the lyophilized**
:00:47 **product.**
:00:49 Q. **Based on your education, experience, your training,**
:00:52 **and the information that you investigated in the course of**
:00:56 **your engagement here, do you have an opinion whether**
:00:59 **Treanda's commercial success, whether Treanda was**
:01:04 **commercially successful and whether that success was related**
:01:08 **to the patented formulations?**
:01:11 A. **Yes. My opinion is that it's definitely a commercial**
:01:15 **success. It's clearly a product that companies would find**
:01:19 **valuable to their portfolio. It sold over 3 billion**
:01:24 **dollars. It has had broad acceptance in the industry, broad**
:01:28 **and rapid acceptance.**
:01:30 **In terms of nexus, there is a link to the**
:01:33 **patents. The patents were important in terms of gaining FDA**
:01:40 **approval, as indicated by Dr. Glick. They met an unmet**
:01:46 **need. And they provide ease of use in the clinic.**
:01:52 **So I think there is both commercial success and**
:01:55 **nexus.**
:01:58 Q. **Isn't it true that physicians prescribe Treanda**
:02:01 **without regard to whether or not there is a patent or**
:02:04 **perhaps without knowledge of the formulations?**
:02:07 **THE COURT: Leading, Mr. Ware.**

:02:10 **MR. WARE: Okay.**

:02:21 **I think I will let it go at that.**

:02:23 **THE COURT: Cross-examine, please.**

:02:29 **MS. HORTON: Thank you, Your Honor.**

:02:30 **CROSS-EXAMINATION**

:02:30 **BY MS. HORTON:**

:03:33 Q. **Good afternoon, Dr. Grabowski.**

:03:35 A. **Hello.**

:03:36 Q. **I am Sara Horton. I represent defendants here, specifically, Hospira.**

:03:43 **Dr. Grabowski, I wanted to touch on a few of the issues you discussed with Mr. Ware earlier just in a few different categories. The first thing I wanted to discuss is what you did prior to forming your opinions in this case.**

:03:56 **So am I correct, Doctor, that you did not review any deposition testimony before coming to your opinions in this case?**

:04:05 A. **I think that's correct.**

:04:07 Q. **And you also didn't review any Cephalon marketing plans?**

:04:11 A. **That's correct.**

:04:11 Q. **Nor any Treanda brand plans?**

:04:15 A. **Yes.**

:04:15 Q. **You also did not review any physician surveys?**

:04:20 A. **Yes.**

Q. **Or any Cephalon internal financial documents concerning Treanda?**

A. **Yes.**

Q. **You did not review any portion of Cephalon's NDA for Treanda?**

A. **I may have reviewed that. I did review it at some point, but I don't remember exactly when.**

Q. **But not before coming to your opinions in this case, before your report? Let me put it that way.**

A. **I think I looked at it after Mr. Hofmann's report.**

Q. **And your opinion came out before Mr. Hofmann's. Right?**

A. **Yes.**

Q. **And your opinion hasn't changed since seeing Mr. Hofmann's report?**

A. **No. But I disagree with most of his opinions.**

Q. **I think we get that.**

You didn't speak to any Cephalon employees while coming to the opinions in your report, either. Correct?

A. **That's correct.**

Q. **Now, you talked some with Mr. Ware about apportionment. Do you know what I mean by that?**

A. **Perhaps.**

Q. **Okay. Let me try to be clear. You talked about how you treated the patents at issue here, the formulation**

:05:24 **patents, as a family?**
:05:27 A. **Yes.**
:05:28 Q. **And you did not analyze the relative contribution of each of those four formulation patents to the commercial success that you have discussed?**
:05:37 A. **That's correct.**
:05:40 Q. **Is it fair to say you also didn't attempt to apportion between the actual asserted claims of the four formulation patents at issue in this case?**
:05:47 A. **Yes.**
:06:10 Q. **Okay. So it's fair to say no commercial success analysis on a claim-by-claim basis?**
:06:19 A. **Yes.**
:06:21 Q. **So -- and you explained in your direct why that doesn't matter to your opinion; true?**
:06:27 A. **Yes. My assignment was to look at this issue in the way that I described.**
:06:40 Q. **Understood. But in the past, you've apportioned your commercial success analysis among different features or among different patents; isn't that right?**
:06:49 A. **I can't recall doing so.**
:06:51 Q. **And you've never apportioned commercial success and nexus based on different features of different products?**
:06:58 A. **No.**
:06:58 Q. **Dr. Grabowski, also going to your nexus opinion and to**

:07:08 **this broad category I will call apportionment, you had an**
:07:12 **understanding that the Orange Book is a listing at FDA of**
:07:15 **patents relevant to a particular approved formulation like**
:07:18 **Treanda?**
:07:19 A. **Yes. A company can list whatever patents it wishes.**
:07:23 Q. **And you're aware that there are three other Orange**
:07:26 **Book patents listed by Cephalon as being relevant to**
:07:29 **Treanda's lyophilized formulation?**
:07:30 A. **I'm aware that there's, yes, three additional patents.**
:07:34 Q. **And you did not analyze those patents in coming to**
:07:36 **your conclusions here today about commercial success?**
:07:39 A. **That's correct.**
:07:39 Q. **And it's true, though, that those patents might have**
:07:42 **some impact on the commercial performance of Treanda?**
:07:45 A. **Yes.**
:07:46 Q. **And you talked a little bit about the bendamustine**
:07:52 **molecule as opposed to the formulation in your direct;**
:07:55 **right?**
:07:56 A. **Yes.**
:07:56 Q. **And you understand that the formulation patents, the**
:08:01 **patents-in-suit, do not actually claim the bendamustine**
:08:04 **hydrochloride molecule itself; is that right?**
:08:06 A. **Yes.**
:08:06 Q. **And there's no compound or API patent here?**
:08:10 A. **That's correct.**

:08:11 Q. **And you have not performed any analysis seeking to**
:08:15 **separate the sales that are attributable to the bendamustine**
:08:18 **hydrochloride molecule as opposed to the patented**
:08:20 **formulation; right?**
:08:21 A. **Right. As I said, I don't think it's a zero-sum game.**
:08:27 Q. **All right. So you have not done that analysis?**
:08:29 A. **That's correct.**
:08:30 Q. **And you also, I think you said that you didn't**
:08:35 **consider what aspects of the patented formulation were**
:08:38 **taught by the prior art?**
:08:39 A. **I have not done a prior art analysis.**
:08:44 Q. **And you didn't review any documents concerning**
:08:47 **attempts by others to develop a bendamustine formulation; is**
:08:50 **that right?**
:08:50 A. **That's correct.**
:08:51 Q. **Okay. You talked a little bit, Dr. Grabowski, about**
:08:58 **FDA approval process for Treanda just generally. And you**
:09:02 **studied the FDA approval process as an academic; is that**
:09:06 **correct?**
:09:06 A. **Yes.**
:09:06 Q. **And you have never worked at FDA?**
:09:08 A. **I've consulted with them, but I've never worked there.**
:09:12 Q. **You've never been an employee?**
:09:15 A. **That's correct.**
:09:16 Q. **You've never participated in meetings with FDA**

:09:19 **concerning new drug applications?**
:09:20 A. **Not directly, no.**
:09:22 Q. **And the same answer for abbreviated new drug**
:09:25 **applications?**
:09:25 A. **Yes.**
:09:26 Q. **And you've never reviewed a drug for safety and**
:09:29 **efficacy at FDA?**
:09:30 A. **That's correct.**
:09:31 Q. **All right. And you are not an expert in FDA stability**
:09:33 **requirements?**
:09:34 A. **I would agree with that.**
:09:36 Q. **And I just want to be sure that I have this. You**
:09:39 **don't have an independent opinion as to whether or not the**
:09:42 **prior art Ribomustin product would have met FDA standards.**
:09:46 **You relied on Dr. Glick for that part of your analysis?**
:09:49 A. **Essentially, I relied on Dr. Glick, but as indicated,**
:09:54 **I think if the prior product had -- if a company could have**
:09:59 **just taken the prior product and gotten FDA approval, it**
:10:02 **would have had a strong motivation to do so. You know,**
:10:06 **companies are looking for new products and this was out**
:10:08 **there for 40 years. So I think that is evidence that it's**
:10:13 **nonobvious.**
:10:14 Q. **Understood. But you don't have an independent opinion**
:10:16 **about whether or not Ribomustin would have met FDA**
:10:19 **standards?**

:10:20 A. **That's correct.**

:10:20 Q. **And you would agree, sir, that regulatory requirements and patentability requirements are different?**

:10:31 A. **Yes.**

:10:33 Q. **And you talked about the orphan drug designation and you looked at, I think it was DTX-161 with Mr. Ware, the sentence that was talking about, please be advised that the active moiety of the drug and not the formulation of the drug is designated.**

:10:34 **Do you remember that testimony?**

:10:47 A. **Yes.**

:10:54 Q. **And your point was that ODE happens when the drug is approved; right?**

:10:57 A. **Among other points, yes.**

:10:59 Q. **Right. But in that letter the FDA specifically said, right, that it's the active moiety of the drug and not the formulation of the drug that is designated; is that correct?**

:11:01 A. **That's the literal wording, but I tried to put it in perspective and what Congress intended.**

:11:02 Q. **Right. But the actual letter that the FDA sent says, "Please be advised that the active moiety of the drug and not the formulation of the drug is designated?"**

:11:02 A. **Yes. That's to the benefit of Cephalon.**

:11:09 Q. **And just to be clear, orphan drug exclusivity, that's**

:11:10

:11:12

:11:15

:11:18

:11:21

:11:21

:11:29

:11:32

:11:35

:11:38

:11:41

:11:44

not determinative of a long-felt need in every case?
A. That is my understanding.
Q. And it is also not determinative of commercial success?
A. That's true also, yes.
Q. All right. And you also talked about priority review as it relates to Treanda, and just to confirm, prior to submitting your report, you didn't review any of Cephalon's correspondence with FDA regarding priority review; is that right?
A. I don't think so.
Q. Okay. Let's, in your binder that I handed you, Dr. Grabowski. Can you please turn to DTX-163?
Mr. Vaughn, can I please show that on the screen as well?
So, Dr. Grabowski, this is a September 19th, 2007 letter from Cephalon to a director at FDA. Do you see that?
A. Yes.
Q. And it relates to the Treanda NDA?
A. Yes.
Q. And do you recognize this as a letter where Cephalon is requesting priority review from FDA?
A. Yes, that appears to be.
Q. All right. So, Mr. Vaughn, if I could focus in on the

last paragraph there, please, on the first page and in the first part of the first paragraph on the second page, the second sentence blown up there, Dr. Grabowski, is:

"During the September 2nd, 2004 guidance meeting with the division, FDA agreed that chlorambucil would be an appropriate comparator drug for Study 02 CLLIII, the pivotal study used in support of the safety and efficacy of this application."

Do you see that?

A. Yes.

Q. And prior to coming to your opinions in this case, you were unaware that that study, 02 CLLIII, is actually a study done on prior art Ribomustin?

A. Well, I'm not sure when I became aware of that, but I am aware that that is the case.

Q. All right. And that study on prior art Ribomustin is the pivotal study used in support of the safety and efficacy of this application for priority review?

A. Yes. It's true that often in clinical trials you use a different formulation because you're dealing with a few hundred patients rather than thousands of patients or tens of thousands once the drug is approved. So when you come to approval, there's -- you can have all formulation that's used in clinical trials that has the active ingredient, but there's also a review process of the chemical formulation

and stability, et cetera.

Q. And just to be clear, this request for priority review submitted to FDA from Cephalon described the pivotal study used in support of the safety and efficacy of this application to be a study on prior art Ribomustin?

A. Yes, but --

Q. Okay.

A. It would not be approved without the drug formulation.

Q. You talked a little bit, Dr. Grabowski, about manufacturing process improvements stemming from the patents-in-suit in your direct. Did I get that right?

A. Yes.

Q. All right. And you aren't saying that there are cost savings to plaintiff that are a basis for commercial success, are you?

A. No.

Q. And you're aware that manufacturing processes aren't -- that the patents, the asserted claims of the patents-in-suit do not relate to manufacturing process improvements; is that right?

A. That's correct.

Q. Okay. And I just want to get some clarity also on your long-felt need testimony.

Is it true that your opinion on -- I'm just trying to understand what the opinion is. Your opinion on

commercial success is not separate from your opinion on long-felt need?

A. It is separate. I mean, commercial success and long-felt need are closely related, but they're separate.

Q. Okay. But you rely on Dr. Leonard for portions of your long-felt need opinion. Is that right?

A. Correct.

Q. And you are not a medical doctor?

A. That's correct.

Q. And you don't have an opinion on long-felt need based on treating patients?

A. Not on treating patients, but on the economic metrics that I analyzed.

Q. And you didn't review clinical data associated with comparisons between Treanda and other drugs?

A. No, I did not.

Q. Okay. Regarding your testimony on the Salmedix-Fujisawa license agreement we just heard, you would agree that the scientific information and data provided by Fujisawa in the license agreement assisted Salmedix in the development and filing of regulatory information for Treanda. Right?

A. Yes.

Q. And you would also agree that that exclusive license

provided a competitive advantage for Salmedix?
A. It provided some competitive advantage but not an insurmountable one.
Q. Did you read Dr. Kabakoff's testimony from last Tuesday?
A. No, I have not.
Q. We will rely on what he said then.
Salmedix announced its relationship with Fujisawa. Right?
A. I believe they did, yes.
Q. To the public.
They announced it in press releases?
A. Yes. That's the typical way you would announce an agreement.
Q. And they announced it in SEC filings?
A. Yes.
Q. Let's look at that.
MS. HORTON: Your Honor, I think we might have to do this the old-fashioned way, because I am not sure that Mr. Vaughn has this.
BY MS. HORTON:
Q. For the record, Dr. Grabowski, I have handed up DTX-1180. Do you recognize this document?
A. I don't believe so.
Q. You are familiar with SEC documents as an economist?

:19:00 A. **Yes.**

:19:00 Q. **And you know that a company is required to disclose material agreements, public companies are required to disclose material agreements in SEC filings?**

:19:11 A. **Yes.**

:19:11 Q. **So this is an S-1 filing with the SEC from Salmedix from April 23, 2004. Right?**

:19:21 A. **Yes.**

:19:21 Q. **I have added some tabs to help us along here, in your copy and mine.**

:19:35 **The first flagged page is Page 35. The second sentence in the section on SDX-105 -- actually, do you understand what SDX-105 means?**

:19:51 A. **Well, it seems self-explanatory. "It's our lead product. It's an intravenously administered small molecule, which we are initially developing for indolent NHL and CLL."**

:20:05 Q. **And it discusses that in May 2003 "We entered into a license agreement with FDE under which we obtained exclusive rights for FDE's clinical trial data and proprietary information to develop, manufacture, and have manufactured, market, and sell SDX-105 in the U.S. and Canada."**

:20:27 **Right?**

:20:28 A. **Yes.**

:20:28 Q. **And then if you turn to the second tab, that's a table of contents describing the attachments to the documents.**

And at Exhibit 10.2 it lists license agreement dated May 1, 2003 between "us and Fujisawa Deutschland GMBH"?

A. **Yes.**

Q. **And then at the third tab, is that the license, in redacted form?**

A. **Yes.**

Q. **One more, Dr. Grabowski.**

Dr. Grabowski, this is DTX-511. Have you seen this document before?

A. **I think I may have. I am not certain.**

Q. **So this is a Salmedix product summary from October 2003. Is that right?**

A. **Yes.**

Q. **And if we could -- Mr. Vaughn, if we could please go to Page 2.**

It starts talking about the product portfolio and under the heading SDX-105, Introduction and Background, the last paragraph on that Page 2, please, there Salmedix is saying, "We believe that Salmedix has a very significant competitive advantage due to our relationship with Fujisawa and that it would be difficult for another group to register the drug in the U.S. before Salmedix because of the transfer of information concerning pharmacology, toxicology, clinical trial databases, et cetera, which we have already received from our partner."

:23:07 **Do you understand "our partner" there to be**
:23:08 **Fujisawa?**
:23:09 A. **Yes. Although I think this is within a few months of**
:23:12 **the initial agreement and they found out that they had to do**
:23:18 **substantial work, essentially, do lab work that led to the**
:23:25 **invention, that they couldn't really use the product that**
:23:28 **they had obtained from Fujisawa.**
:23:32 Q. **And we just looked at documents showing that the**
:23:37 **clinicals that supported the CLL indication with FDA were**
:23:40 **actually done with the prior art Ribomustin from Fujisawa.**
:23:44 **Right?**
:23:44 A. **The clinicals for CLL, along with other information**
:23:52 **that was submitted to the FDA, but not the chemical and**
:23:57 **manufacturing approvals.**
:23:58 Q. **Right. The underlying clinical data was performed**
:24:02 **with the prior art Ribomustin?**
:24:03 A. **Some of it, yes, it was useful.**
:24:07 **MS. HORTON: No further questions, Your Honor.**
:24:09 **THE COURT: Redirect, Mr. Ware.**
:24:10 **MR. WARE: No, Your Honor.**
:24:11 **THE COURT: Thank you, Doctor.**
:24:11 **(Witness excused.)**
:24:22 **THE COURT: Mr. Wiesen.**
:24:23 **MR. WIESEN: Your Honor, with the conclusion of**
:24:30 **Dr. Grabowski's testimony, Cephalon rests its rebuttal case.**

:24:34 **THE COURT: Okay. So, counsel, where are we now?**

:24:38 **MR. WIESEN: I believe the defendants are going to call their three secondary considerations witnesses tomorrow. And we would be done for today.**

:24:45 **MS. HORTON: I agree with that, Your Honor.**

:24:49 **THE COURT: Why don't we recess.**

:24:51 **(Court recessed at 3:15 p.m.)**

:24:52 **- - -**